Depression: Can we predict who will relapse?

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Thesis declaration form

I confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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OVERVIEW

This thesis addresses risk factors and proposed mechanisms to explain relapse to depression. Volume 1 comprises three parts:

Part 1 is a literature review consisting of meta-reviews of systematic and non-systematic reviews of studies reporting on risk factors for relapse to depression, and a systematic-review of neuroimaging and experimental studies investigating risk factors for relapse and potential mechanisms of action of these risk factors. The reviews found that only residual symptoms of depression at the end of treatment and childhood maltreatment were sufficiently evidenced as predictors of relapse and neither have great clinical utility. A number of psychological and neuropsychological factors were suggested to play a role in conferring risk for relapse. Considering the inter-relationships between these factors the reviews were used to propose a conceptual framework which may be used to help guide future research into relapse to depression in adults.

Part 2 is an empirical paper in which data were analysed from service users of a primary care mental health service to identify risk factors for relapse and for the presence of residual symptoms, and survival analysis methods were used to determine when relapses occur most often and what factors impact survival. In addition, a prospective cohort study was formed to investigate the relationship between cognitive control and depressive symptoms. The findings confirmed that cognitive control can be used to predict residual symptoms of depression post-treatment and therefore potentially to predict relapse.

Part 3 is a critical appraisal focussing on the theoretical reasons as to why studying relapse in a manner as used in the prospective study is so important and discusses the logistical difficulties conducting such research in the current context of NHS services and of the D.Clin.Psy research project. Methodological decisions made that impacted upon the research process are discussed and reflective conclusions are offered.

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PART 1: LITERATURE REVIEW

Identifying Risk Factors for Relapse to Depression and Considering How They Operate: A Three-Stage Systematic Review of the Literature

Abstract

Aims: To determine what factors confer risk for relapse to depression after acute-phase treatment in adults and to consider the mechanisms by which they might operate. **Methods:** Three separate reviews were conducted: Study 1 included only systematic reviews; Study 2 included non-systematic reviews; and Study 3 included neuroimaging and experimental studies. Quality ratings in Study 1 were based on the AMSTAR, along with items from PRISMA and the Cochrane Reviewer's Handbook; study quality was not assessed in Study 2; and criteria developed by Kmet, Lee and Cook (2004) were used for Study 3. Each of the three studies involved a narrative synthesis with the formation of a matrix to consider each risk factor identified as associated with relapse/recurrence from the perspective of each reviewed study, and a conceptual framework was then built on the basis of findings from all three studies. **Results:** Seven articles were reviewed in Study 1, 21 in Study 2, and 15 in Study 3. Only the presence of residual symptoms of depression after treatment and childhood maltreatment were well supported with strong evidence from high quality systematic reviews as risk factors for relapse to depression. A number of factors that to date had not been systematically reviewed were identified as conferring risk for relapse, but these were not supported in the literature with the same degree of strong evidence. **Conclusions:** The consensus view that only residual depressive symptoms and a history of multiple previous episodes confer risk for relapse to depression (Campbell, 2009) needs amending. There were no factors supported by high quality reviews able to provide strong evidence that have utility in guiding the treating clinician in reducing their patient's risk of relapse/recurrence to depression. A number of affective and information processing biases were suggested to play a role relapse. Considering the inter-relationships between these factors a conceptual framework was built which may help guide future research into relapse/recurrence to depression in adults. (For a full abstract in the format outlined by PRISMA see Appendix I).

Introduction

Depression is considered to be the single most burdensome disease world-wide in terms of years of life lost to disability (Murray & Lopez, 1996; Prince et al., 2007). This is due to the fact that depression is highly prevalent, results in significant functional impairment, increases the risk of suicide and of comorbid physical health problems, and as many as 80% of sufferers will have more than one episode (Judd, 1997; Kessler & Wang, 2009; Mueller et al., 1999; Murray & Lopez, 1996; Roiser, Elliot & Sahakian, 2012). Indeed it has been reported that the mean number of episodes of depression per sufferer is approximately four, with a mean duration of approximately 20 weeks per episode (Judd, 1997). While depression can occur as an acute condition (Angst, Kupfer & Rosenbaum, 1996) it is widely considered by most commentators to follow a 'relapsing-remitting' course (e.g. Burcusa & Iacono, 2007), with disabling sub-syndromal symptoms periodically occurring in between discrete episodes (Angst et al., 1996). Depression and the relapse or recurrence of it therefore result in a heavy burden on health services, with this now a major public health concern both within the UK (e.g. Public Health England, 2013) and internationally (e.g. Prince et al., 2007; World Health Organization [WHO], 2009).

The consensus view of relapse/recurrence (used interchangeably throughout this article) to depression as defined by Campbell's Dictionary of Psychiatry (2009) is that only two factors are reliably known to influence risk for relapse: having residual sub-threshold depressive symptoms at the end of acute phase treatment, and having had two or more depressive episodes prior to the index episode. It is also reported that with increasing episodes relapse becomes autonomous from stressful life events (Campbell, 2009). So, despite more than half a century of active research into treating depressive episodes, preventing relapses and recurrences, and understanding the risk factors for depression, we are still a long way from predicting who will relapse following treatment (Beckerman & Corbett, 2010; Hughes & Cohen, 2009; Roiser, et al., 2012). It is therefore unsurprising that

there is no treatment currently able to provide more than a small-to-medium effect size for preventing depressive relapses (Clarke, Mayo-Wilson, Kenny, & Pilling, in press).

Several experts in the field have suggested that part of the difficulty in finding more successful treatments for preventing depressive relapses is due to a lack of clarity about what it is that actually confers risk for relapse and how identified risk factors can be utilised in the consulting room (e.g. Burcusa & Iacono, 2007). In addition, many studies that have investigated relapse have been hampered by methodological problems or inconsistencies (Monroe & Harkness, 2011).

Early studies into these phenomena did not use consistent definitions of relapse and recurrence (Beshai, Dobson, Bockting, & Quigley, 2011). However, a majority of studies now follow the criteria suggested by Franck et al. (1991) who defined relapse as 'a return to the depressive episode after remission but without reaching a full recovery (i.e. less than eight weeks symptom free)', and recurrence as 'the onset of a new depressive episode after having fully recovered from a previous one (i.e. being symptom free for eight or more weeks)' (Frank et al., 1991). More recently though, it has been suggested that even these definitions may have biased research by failing to discriminate those patients with a first lifetime episode of depression from those with a history of multiple previous depressive episodes. As such, researchers following these criteria may have been combining results of those that may never suffer a relapse of depression with those that have already suffered relapses. Combining results together in such a way may have led to spurious conclusions about the course of depression and what confers risk for relapse or recurrence (Monroe & Harkness, 2011).

Most studies seeking to understand or identify risk factors for depressive relapse have involved prospective longitudinal follow-up of patients after they have presented with a depressive episode at a treatment centre and have either remitted or fully recovered. However, some studies have included only those with unipolar depression whilst others

have included those with recurrent episodes of depression in the context of bipolar disorders. This is particularly relevant to studies of clinical samples as bipolar disorders are more common in these populations than in the general population as a whole. Further difficulty has arisen when assessing the findings of randomised controlled trials as many have required participants to be free from comorbid 'Axis 1' and/or 'Axis II' disorders, and given that 45% of people with any mental disorder have more than one separate mental health diagnosis (Kessler, Chiu, Demler & Walters, 2007), findings from such studies may not be applicable to a large number of patients seen in health services (Kessler et al., 1996). Many large observational studies have used hospital readmission rates to determine when a study participant has suffered a relapse/recurrence. However, such methods may introduce significant selection bias as this might only represent the most severe of cases or those with greatest access to healthcare, missing large numbers of others that are either not receiving care at all, or not as an inpatient (Hatch et al., 2011; Hatch & Thornicroft, 2012). Further, such naturalistic studies have often failed to account for differences in maintenance treatments and their effects on the rate of recurrence (Burcusa & Iacono, 2007), and many of the trials and observational studies investigating relapse/recurrence have suffered from high attrition rates suggesting yet further bias in the interpretation of their results (Burcusa & Iacono, 2007).

In addition to the above there has been debate about whether or not recurrence represents a phenomenon which can be understood and eventually prevented, or whether it represents a sub-type of depression naturally leading to multiple episodes occurring over the life-course (Burcusa & Iacono, 2007). The concept of depression as a diagnosis has been repeatedly questioned and many researchers have attempted to differentiate subtypes of depression with various nosologies, including recurrent depression and many others (e.g. anxious depression, atypical depression, endogenous depression, melancholic depression, and reactive depression). However, separating cases into these proposed subtypes has led

to few advances in treating depression, either in resolving the acute episode or in preventing relapse/recurrence (Monroe & Harkness, 2005; 2011). The heterogeneity within the diagnostic category of depression suggests a number of different causal pathways and prognoses (National Institute for Clinical Excellence [NICE], 2004). The use of a single diagnostic label for the heterogeneous experiences that can occur within this diagnosis may have limited the ability of researchers and clinicians in finding more successful solutions to treating and preventing relapse (NICE, 2004).

It may be the case that the difficulty in coming to conclusions about what does and does not confer risk for depressive relapse is due in part to the restrictions of using disease classification systems that group disorders based on clusters of symptoms rather than either behavioural/functional experiences or underlying biology. Such systems do not lend themselves to greater understanding of the mechanisms behind the separate experiences within the cluster of symptoms (Cuthbert & Insel, 2010; Insel et al., 2010; NICE, 2004). However, given the above outlined methodological difficulties in this literature, it is not surprising that researchers have thus far struggled to determine exactly what explains relapse/recurrence to depression and how this knowledge can be utilised. Despite this, there is a large body of literature to draw upon and means of rigorously and systematically summarising and synthesising the data available may yet deliver a basis for understanding relapse/recurrence and a conceptual framework to be tested in new research in this field.

The present study therefore aimed to summarise and synthesise findings of studies that have reported either on risk factors for depressive relapse/recurrence or those that have sought to explain the mechanisms underlying the action of these risk factors. This was with a view to developing a conceptual framework that may help us better understand the phenomena of depressive relapse and recurrence, and consider how the body of evidence can be built in future studies whether or not newer nosological systems for mental disorders are developed.

Study 1

Aim

The National Health and Medical Research Council of Australia (NHMRC) suggest that in developing clinical guidelines the best evidence for the prognosis or aetiology of disorders comes from systematic reviews of prospective cohort studies, with the next greatest level of evidence coming from systematic reviews of retrospective cohort studies or randomised controlled trials (RCTs), and then from pseudo-randomised trials, non-randomised trials, and case-control studies (Coleman et al., 2009). The aim of the present study was therefore to conduct a meta-review of systematic reviews of prospective cohort studies, RCTs, retrospective cohort studies, pseudo-randomised trials, non-randomised trials, or case-control studies that reported on risk factors for relapse/recurrence to depression in adults. The findings from this meta-review would then be considered in light of the consensus view on relapse to depression (e.g. Campbell, 2009), to determine whether or not this may be amended or expanded based upon the findings of those studies considered to have the greatest level of evidence for the aetiology and prognosis of depressive relapse/recurrence.

Methods

A meta-review of systematic reviews was conducted in accordance with the preferred reporting method for systematic reviews (PRISMA) guidelines wherever possible (Moher, Liberati, Tetzlaff & Altman, 2009). However, no protocol was registered for this review.

Search Strategy

Studies were identified by using a combination of keyword and subject heading searches on the following bibliographic databases: Cochrane Database of Reviews (searched on 16th November 2013), Embase 1947 to 2013 Week 47, Ovid MEDLINE 1946 to November Week 3 2013, Prospero (searched on 16th November 2013), PsycEXTRA 1908 to November 16,

2013, and PsycINFO 1806 to November Week 3 2013. Each database was searched individually and results were combined before removing duplicates. Search terms included variations of phrases such as “depression” or “major depression” or “major depressive episode” or “MDD” or “unipolar depression” or “depressive episode”, and “relapse” or “recurrence”, and in the relevant databases the searches were run to include terms such as “review”, “systematic review” or “meta analysis”. An example of the search conducted for articles in PsycINFO is listed in Table 1. A full list of all the searches conducted and results thereof can be found in Appendix II.

Study Selection

All search results were reviewed by a single reviewer reading through study titles to remove any clearly non-relevant articles based on the inclusion and exclusion criteria listed below. The remaining study abstracts were read and judged as either relevant to this review, possibly relevant, or definitely not relevant, based on inclusion and exclusion criteria. All studies deemed to be either relevant or possibly relevant were read in full and independently judged against inclusion and exclusion criteria by two reviewers. Disputes were resolved by consensus and by consultation with a third reviewer where necessary. Hand searching of the references from all the included studies was conducted to identify studies missed in the bibliographic database searches. Any possibly relevant or relevant studies were then processed using the same procedure as detailed above.

Table 1.
Search strategy and results for finding articles in PsycINFO.

PsycINFO 1806 to November Week 3 2013	N
1. exp major depression/ or exp "depression (emotion)"/	111027
2. recurrent depression/	617
3. exp Relapse Prevention/ or exp "Relapse (Disorders)"/	6945
4. 1 or 2	111027
5. ((relapse or recurrence) adj5 depressi*).mp.	1939
6. 3 and 4	1133
7. 6 or 5	2229
8. 7	2229
9. limit 8 to (human and english language and journal article)	1598
10. bipolar disorder/ or affective psychosis/ or mania/	21943
11. exp Schizoaffective Disorder/	2568
12. 10 or 11	24023
13. 9 not 12	1382
14. exp Child Psychopathology/	1426
15. 13 not 14	1381
Substance abuse.mp	27069
exp Drug Abuse/	85848
exp Alcohol Abuse/	38362
16 or 17 or 18	85848
15 not 19	**1320**

Inclusion Criteria: Studies were included if: 1) they were systematic reviews (with or without any quantitative synthesis) of RCTs, quasi-randomised controlled trials, non-randomised controlled trials, prospective cohort studies, retrospective cohort studies, or case-control studies; 2) they provided data on at least one explanatory factor for relapse/recurrence to depression; 3) studies reviewed in the article under consideration had some longitudinal measurement of depressive symptoms and either a clinical interview to determine status of onset, remission, recovery, relapse, and/or recurrence, or used well validated interviewer-rated or self-report measure(s) of depressive symptoms; 4) they reviewed studies of adults aged 18 years or older; and 5) were journal articles published in the English language.

Exclusion Criteria: Studies were excluded if: 1) they were not systematic reviews; 2) they provided no data on explanatory factors associated with relapse/recurrence to

depression; 3) they reviewed studies of populations with bipolar disorder, psychotic depression, seasonal affective disorder, depression secondary to organic brain disorders, or if they focussed on relapse to other conditions (such as drug or alcohol misuse disorders) comorbid to depression; 4) they were reviews of studies exclusively of children or adolescents (i.e. those younger than 18 years old), including studies of the impact of parental depression on children, or of studies of older adults only and/or factors relevant only to a geriatric population; 5) they were non-journal articles; and 6) if they were not published in the English language.

Data Extraction

Data on the search strategy, databases searched, terms used for searching, inclusion and exclusion criteria, as well as methods of quantitative synthesis (where applicable) were extracted from each included study by a single reviewer. In addition, data on the studies included in the review and the main results of relevance to associations between identified factors and relapse/recurrence to depression, were also extracted from each included study by a single reviewer. The latter information was used to build a matrix such that every proposed factor could be considered from the perspective of each included study. The strength of association between the factor and relapse/recurrence as reported in each study by the study authors was entered into each cell of the matrix.

Rating Study Quality

Quality ratings for all included studies were established independently by two reviewers, with disputes resolved by consensus or by consultation with a third reviewer where necessary. The 'a measurement tool to assess the methodological quality of systematic reviews' (AMSTAR) rating system (Shea et al., 2007) was used to judge the quality of the included studies, with further consideration given to factors listed in the PRISMA statement (Moher et al., 2009) and factors identified in the Cochrane Reviewer's Handbook (Higgins &

Green, 2008) regarding preferred reporting standards and assessment of bias in included studies. The AMSTAR consists of 11 items listed as questions, for example: 'Was there duplicate study selection and data extraction?'. For each item one of four responses must be given 'Yes', 'No', 'N/A', or 'Cannot Answer'. The authors of the AMSTAR do not suggest a summary score or categorical statement about the quality of the reviewed studies.

The AMSTAR is the best available method for judging the quality of systematic reviews of the types included in the present study (Shea et al., 2007). However, in order to bring a common structure to the interpretation of the AMSTAR quality ratings the categories suggested by Guyatt and colleagues in the GRADE rating system (Guyatt et al., 2008) (favoured by the National Institute for Clinical Excellence as a means of judging quality of RCTs in systematic reviews) were used. Each study was labelled as fitting into one of the following four categories: High quality – suggesting that further research is very unlikely to change the level of confidence in the estimate of the effect; Moderate quality – suggesting that further research is likely to have an important impact on the level of confidence in the estimate of the effect; Low quality – suggesting that further research is very likely to impact upon confidence in the estimate of effect; and Very low quality – suggesting that any estimate of effect is particularly uncertain (Guyatt et al., 2008). Studies were judged as being of very low quality if very few or none of the AMSTAR items were answered 'yes' and as low quality if more of the AMSTAR items were answered 'no' than were answered 'yes'. Studies were judged as of moderate quality if marginally more AMSTAR items were answered 'yes' than 'no' or if many more were answered 'yes' than 'no' but the study was not awarded a 'yes' answer to the questions relating to study selection or quality ratings. In addition, if the reviews did not give at least cursory reasons as to why studies were excluded from the review (PRISMA – Moher et al., 2009), if they included RCTs that did not blind investigators to participant allocation, and/or if they did not deal appropriately with the likely sources of bias in their methods and/or the

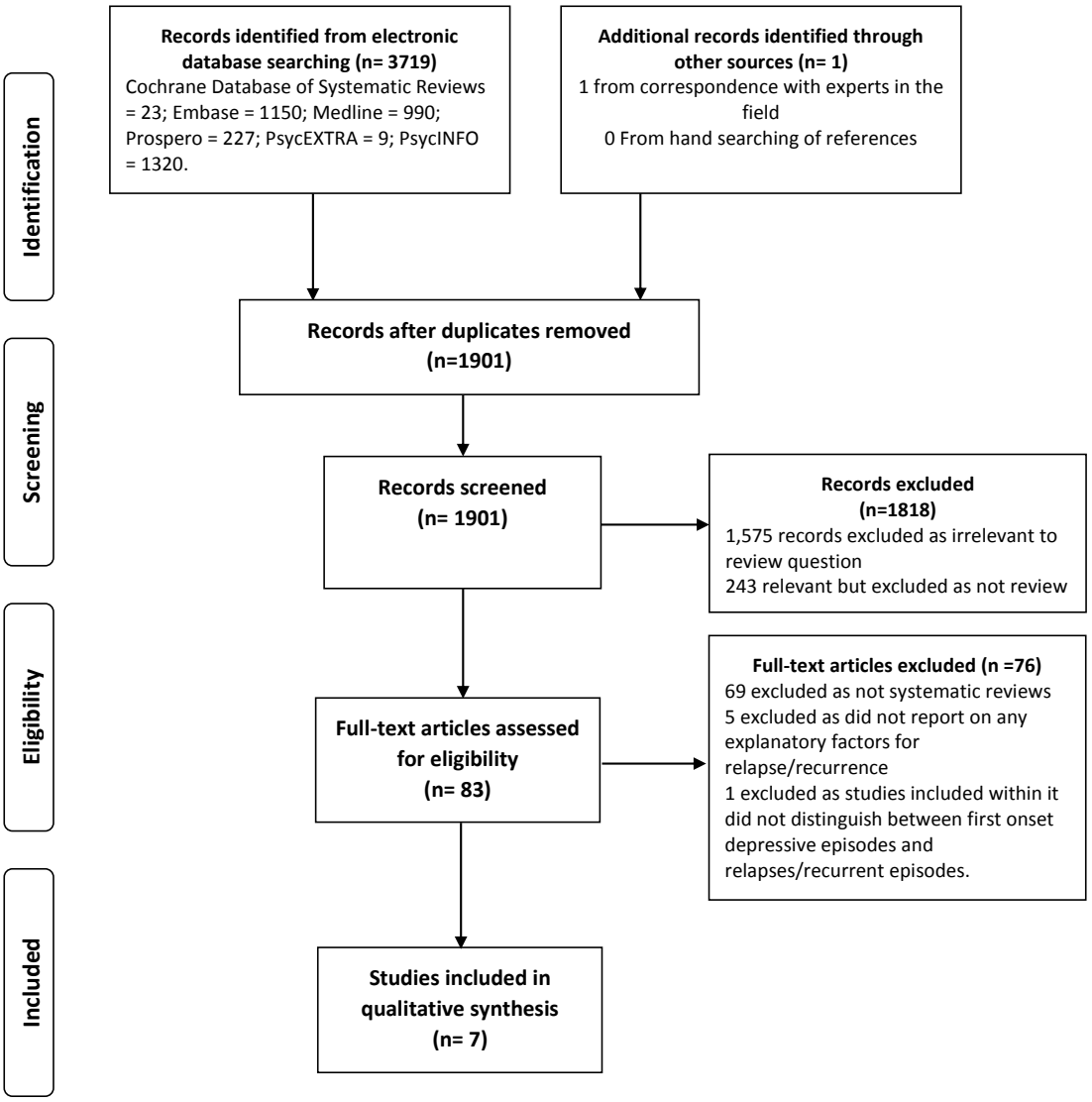
interpretation of their results (Cochrane Reviewer's Handbook – Higgins & Green, 2008), they were rated as of moderate quality. If these latter criteria were met and studies had many more 'yes' answers from the AMSTAR items than 'no' answers then they were rated as high quality.

Results

Six studies were identified as meeting inclusion criteria from the bibliographic database searches and one study was added after consulting experts in the field for unpublished reports, giving a total of seven studies included in the present review (see Figure 1).

Figure 1.

Flow diagram of study selection.



Characteristics of Included Studies

Of the seven systematic reviews included in the present study, three reviewed cohort studies, two reviewed RCTs of non-pharmacological relapse prevention therapies, one reviewed both RCTs and quasi-randomised controlled trials (of any psychological relapse prevention treatment), and one reviewed both cohort studies and clinical trials (of either pharmacological or non-pharmacological relapse prevention treatments). All included articles reviewed studies of adults aged 18 or over, whilst two articles also included studies of children or adolescents; for the latter two, details pertaining only to adults 18 or over were used for the present review. Full details of the methods adopted by each included review can be found in Appendix III. Details regarding the reviewed studies in each review, the participants, interventions, comparators, and outcomes, along with the main results of each review in relation to factors associated/not associated with relapse are outlined in Table 2.

Study Quality

Quality judgements were made at the level of the review not of the studies included in each review. Only three of the included reviews reported on the quality of the studies reviewed therein: Clarke et al. (in press) reported that the majority of the 24 studies they reviewed were of 'low quality'; Feng et al. (2012) reported that the 32 studies they reviewed were all of 'good quality'; and Kok et al. (2013) reported that the four studies they reviewed were of 'low-to-moderate quality'.

Quality of reviewed studies: Of the seven included reviews three were judged to be of high quality (See Table 3) (Clarke et al, in press; Feng et al., 2012; Nanni, Uher & Danese, 2012), though all of these focussed only on narrow areas related to relapse to depression rather than considering multiple potential explanatory factors. The Clarke et al. (in press) review looked only at non-pharmacological relapse prevention treatments and aimed to consider the relative efficacy of each type of treatment in preventing relapse. The

only factor of relevance to the present review was the presence or absence of sub-threshold residual symptoms of depression after acute phase treatment, for which they reported some evidence of a positive association with relapse such that those with residual symptoms were more likely to relapse than those without residual symptoms. Feng et al. (2012) investigated the factors impacting on the efficacy of group based CBT as a relapse prevention treatment and focussed mainly on the treatment related factors impacting upon this. As with the Clarke et al. study (in press), they also investigated the impact of having residual symptoms on the efficacy of the treatment and found very strong evidence for a positive association between the presence of residual symptoms and relapse. There was some overlap between the studies reviewed by Clarke et al. (in press) and Feng et al. (2012) with seven studies included in both of these reviews.

Feng et al. (2012) also looked at the impact of having multiple previous depressive episodes and found no association between this and the risk of relapse. Nanni and colleagues (2012) investigated the impact of various forms of childhood maltreatment and found very strong evidence of a positive association between suffering any form of childhood maltreatment and greater risk of relapse/recurrence to depression.

Of the remaining four reviews one was rated as moderate quality (Kok et al., 2013). This too had a very narrow focus investigating the impact of comorbid physical health problems on relapse, and finding no evidence of an association between the two. The three reviews that aimed to consider multiple risk factors for relapse/recurrence were all rated as low quality (Hardeveld, Spijker, De Graaf, Nolen, & Beekman, 2010; Hughes & Cohen, 2009) or very low quality (Beshai et al., 2011) and the results from these are therefore considered with caution. Beshai et al. (2011) reported inconclusive evidence related to residual symptoms despite including seven of the same studies as Feng et al. (2012) and 13 of those reviewed by Clarke et al. (in press). Otherwise there was little overlap in the studies included in each review.

Table 2.

Data extracted from included systematic reviews.

Reviewed Studies	Number of included studies and study design	Study population	Intervention	Comparisons of relevance	Main outcomes and how recorded	Main results relevant to relapse/recurrence
Beshai et al., 2011	20 RCTs, 4 non-randomised controlled trials	Adults with current depression	Any psychological therapy aimed at relapse prevention	Relapsers Vs recovered/remitted patients in different intervention groups of trials.	Most studies used SCID-I or equivalent, others used self-report e.g. BDI + interviewer rated e.g. HRSD	Role of residual symptoms is inconclusive. Evidence that cognitive vulnerability corresponds to deficits in neural circuitry and abnormalities in certain brain regions implicated in emotional processing. Chronic interpersonal stress (as opposed to cognitive or personality factors) only variable significant for depressive relapse. Access to negative thinking may be important for recurrent depression.
Clarke et al., in press	24 RCTs. 19 included in meta-analysis combined N= 1463	Adults with at least one past episode of MDD who had partially or fully recovered	Any non-pharmacological intervention	Between groups, relapsers Vs non-relapsers	DSM/RDC diagnoses of depression; HRSD/SCID/MADRS degree of symptomology during follow-up	MBCT, CBT, and IPT are all efficacious as relapse prevention treatments. In included trials risk reduced by between 22% and 25% compared to controls.
Feng et al., 2012	32 RCTs. 19 included in meta-analysis, combined N=2152	Adults 18+ with MDD	Group CBT	Relapsers vs Non-relapsers	Relapse rate, and rate difference. Relapses recorded by SCID/RDC/DSM/ICD criteria	Residual symptoms increased the risk of relapse. Past relapse episodes, experience of the therapist, type of control group, group size, group manual, therapy frequency, and take-home assignments showed no significant differences in effect.
Hardeveld et al., 2010	27 naturalistic cohort studies	Adults with MDD		Non-recurrers within settings; rates compared across settings.	Clinical Interview or rater checklists based on RDC/DSM/ICD	Two main predictors of recurrence: the number of previous episodes and residual symptoms after recovery. Gender, SES, and civil status, and age at first onset do not predict recurrence. The evidence is inconclusive for: neuroticism, lack of social support, severe life events, comorbid axis I and II disorder, the severity and duration of the previous episode, younger age of onset, family history of MDD and psychosocial impairment.
Hughes & Cohen, 2009	12 long-term prospective cohort studies (24 publications)	Adults 18+ with depression, dysthymic disorder or mood disorder	No specific intervention.	Recurrence Vs non-recurrence	HAM-D, BDI, SCID, and other clinical interviews based on DSM-III and DSM-IV, or ICD-10	There was inconsistent evidence for episode duration and symptom severity as predictors.

Kok et al., 2013	3 Prospective cohort studies, 1 retrospective cohort study	Adults with MDD and Chronic Somatic Illness (3 studies) children (aged 8-13) with MDD and CSI (1 study)	No specific intervention.	Adults with MDD without Chronic Somatic Illness in three of the four studies, children (aged 8-13) with MDD without CSI in the other.	Clinical Interview or rater checklists based on RDC/DSM/ICD	No indication that comorbid somatic illness was associated with a greater risk for recurrence.
Nanni et al., 2012	16 Epidemiological studies: 9 Population health surveys with prospective follow-up, 7 clinical sample surveys with prospective follow-up, combined N=23,544. 10 Clinical Trials (2 controlled observational studies; 6 RCTs; 2 non-randomised controlled trial) combined N = 3,098.	Adults 18+ in Epidemiological studies (except one study 15+), Adolescents and adults of all ages in RCTs.	In Clinical Trials - CBT and/or Anti-depressants	Recurrence Vs non-recurrence; Duration of episode	HAM-D and Number of episodes. Of Epidemiological studies 7 investigated recurrence (9 investigated persistence).	Maltreated individuals were approximately twice as likely as those without a history of childhood maltreatment to develop recurrent or persistent depressive episodes. Confounding by age at onset was unlikely. From Clinical Trials: maltreated individuals were more likely than those without a history of childhood maltreatment to show poor treatment outcome.

Abbreviations: BDI – Beck Depression Inventory; CBT; cognitive behaviour therapy; CI – confidence interval; CSI –chronic somatic illness; DSM-IV/DSM-III – Diagnostic and Statistical Manual of Mental Disorders $4^{th}/3^{rd}$ Edition; HAM-D – Hamilton depression rating scale; HRSD - Hamilton rating scale for depression; ICD-10 – International Classification of Diseases 10^{th} Edition; IPT – interpersonal psychotherapy; MADRS – Montgomery-Asberg Depression Rating Scale; MBCT –Mindfulness based cognitive therapy; MDD – major depressive disorder; MDE – major depressive episode; RCT – randomised controlled trial; RDC – research diagnostic criteria; SCID – Structured Clinical Interview for DSM-IV.

Matrix of factors associated/not associated with relapse

The only factors to be endorsed as positively associated with relapse/recurrence for which there was strong evidence from high quality reviews were the presence of residual symptoms post-treatment and suffering childhood maltreatment. Only one of the reviews reporting these effects also reported that the studies reviewed therein were of good quality; the studies included in the other reviews to report on these factors were either considered to be 'low quality' or the quality of them was not reported on.

There was no association found between having multiple previous episodes and risk of relapse in the only high quality review to examine this, and all the studies included in this review were reported to be of 'good quality' (Feng et al., 2012). One low quality review (Hughes & Cohen, 2009) found the same result whilst a second (Hardeveld et al., 2010) found the opposite; a positive association between multiple previous episodes and increased risk of relapse. However, only one of the studies included in the latter review was also included in the high quality review, so the respective results are for the most part based on different studies.

Most other factors were found to have no association with relapse or the evidence for them was inconclusive. The low and very low quality reviews suggested some links between a number of other factors and relapse, though there was no strong evidence for these associations. Most studies commented on the impact of stress on the risk for relapse, though there was no agreement on the mechanism for this with some reviews suggesting that relapses occur autonomously from stress whilst others suggested stressful life events were important in triggering relapses, in particular stress in the interpersonal domain (see Table 4 for details).

Table 3.

Rating of study quality for included systematic reviews using AMSTAR and items from PRISMA and the Cochrane Reviewer's Handbook.

Study Citation	Research question and inclusion criteria established prior to review?	Were there at least 2 independent data extractors and a consensus procedure for disagreements?	2+ databases searched? Keywords/MeSH terms stated, searches supplemented by hand searching?	Was publication status used as an inclusion criteria?	List of included and excluded studies provided?	Characteristics of included studies provided?	Scientific quality of included studies assessed and documented?	Was scientific quality of included studies used appropriately in formulating conclusions?	Were the methods used to combine findings of studies appropriate?	Was the likelihood of publication bias assessed?	Was the conflict of interest stated? - both in the review and in the included studies	*At least cursory reasons given for exclusion of studies **	*Investigators blinded to participant allocation in included clinical trials#*	*Fully assessed and dealt with sources of bias#*	*Overall Quality Rating*
Beshai et al., 2011	Yes	Can't answer	No	Can't answer	No	No	No	N/A	N/A	No	No	No	No	No	Very low
Clarke et al., in press	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Feng et al., 2012	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	High
Hardeveld et al., 2010	Yes	Yes	Yes	Yes	No	No	No	N/A	N/A	No	No	Yes	N/A	No	low
Hughes & Cohen, 2009	Yes	No	Yes	Yes	No	Yes	No	N/A	N/A	No	Can't answer	Yes	N/A	No	low
Kok et al., 2013	Yes	Yes	Yes	Can't answer	No	Yes	Yes	No	Can't answer	No	No	Yes	N/A	No	Moderate
Nanni et al., 2012	Yes	Yes	Yes	Can't answer	No	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes	High

All items are from AMSTAR unless otherwise stated; * From PRISMA; # From Cochrane Reviewer's Handbook.

Table 4.

Factors associated and not associated with relapse/recurrence to depression in adults and strength of associations as reported in each of the included systematic reviews.

Study citation and quality rating	**Factors investigated for their association with relapse/recurrence**							
	Residual Symptoms	Number of Previous Episodes	Severity of last episode	Duration of last episode	Younger Age at first onset	Neuroticism	Demographics - Sex, Marital Status, Socio-economic status, Educational History	Other
Beshai et al., 2011 Very low quality	~					=		Interpersonal Stress ++; Cognitive Reactivity +; Cognitive Biases +; Rumination +; Negative Thought Content = =
Clarke et al., in press High quality	+							
Feng et al., 2012 High quality	+++	= = =						For Group CBT: Group size, type of manual, frequency of sessions, and whether using take-home assignments or not, all = =
Hardeveld et al., 2010 Low quality	++	++	+	=	~	~	= =	Low social support =; Psychosocial impairment post depression +; Severe life events ~; Comorbid Axis I ~ or Axis II ~; Family history of Affective Disorders =
Hughes & Cohen, 2009 Low quality		= =	= =	= =	=		= =	
Kok et al., 2013 Moderate quality								Comorbid Physical Illness = = =
Nanni et al., 2012 High quality					=			Childhood Maltreatment +++

Key: +++ Strong evidence for positive association with relapse; ++ good evidence of positive association with relapse; + some evidence/suggestion of positive association with relapse
=== Strong evidence for no association with relapse; = = good evidence of no association with relapse; = some evidence/suggestion of no association with relapse
~ Inconclusive evidence regarding association with relapse.

Discussion

From the seven included systematic reviews there were only two factors that we can definitively conclude are positively associated with relapse/recurrence. These are the presence of sub-threshold residual symptoms of depression at the end of acute phase treatment, and having suffered some form of maltreatment during childhood. It is likely that there is no association between having multiple previous episodes and relapse, although one low quality review found good evidence for a positive association between the two. Certain groups of factors related to cognitive processing of information (rather than the content of cognitions) and interpersonal stress were suggested to be associated with greater risk for relapse but without good evidence to support this.

The results of this study differ from the consensus view of relapse to depression (e.g. Campbell, 2009), suggesting a need to reconsider the 'conventional wisdom' that risk of relapse is increased only by the presence of residual symptoms and in those with multiple previous episodes of depression (e.g. Campbell, 2009). However, neither of the two factors found to be positively associated with relapse here lend themselves to guiding the clinician seeing a depressed patient in their consulting room to deliver a treatment programme that will reduce the risk of future relapse; they therefore have limited utility. There were several factors suggested to be associated with relapse for which it is conceivable that a mechanism for their action may be able to help guide clinicians (e.g. cognitive reactivity and interpersonal stress – Beshai et al., 2011). However, there is little evidence to support their association(s) with relapse. Further, the reviews included in this study did not focus on these factors in any great detail so were not able to propose any such mechanisms. Therefore it may be that other non-systematic reviews, which focussed specifically on these factors, may give greater insight into the mechanisms behind relapse to depression and help guide thinking about how to tackle it in the consulting room.

Study 2

Aim

Given the paucity of systematic reviews investigating factors associated with relapse to depression and the limited utility of the factors found from such reviews, the present study aimed to perform a meta-review of non-systematic reviews reporting on factors associated with relapse/recurrence to depression in adults.

Method

Using the same searches and procedure for identification of studies conducted for Study 1 but applying a different set of inclusion and exclusion criteria (detailed below), non-systematic reviews reporting on factors associated with relapse to depression and/or the mechanism of action for such factors were identified and data were extracted for this review.

Inclusion Criteria: Studies were included if: 1) they were non-systematic reviews; 2) they reported on at least one explanatory factor for relapse/recurrence to depression; 3) they reviewed studies of adults 18 years or older; and 4) they were journal articles published in the English language.

Exclusion Criteria*:* Studies were excluded if: 1) they were not review articles or if they were systematic review articles; 2) they only reviewed articles covered in the systematic reviews included in Study 1; 3) they did not report on explanatory factors associated with relapse/recurrence to depression; 4) they reviewed studies of populations with bipolar disorder, psychotic depression, seasonal affective disorder, depression secondary to organic brain disorders, or if they focussed on relapse to other conditions (such as drug or alcohol misuse disorders) comorbid to depression; 5) they were reviews exclusively of studies of children or adolescents (i.e. those younger than 18 years old), including studies of the impact of parental depression on children, or of studies of older

adults only and/or factors relevant only to a geriatric population; 6) they were non-journal articles; and 7) they were not published in the English language.

Data extraction and quality ratings

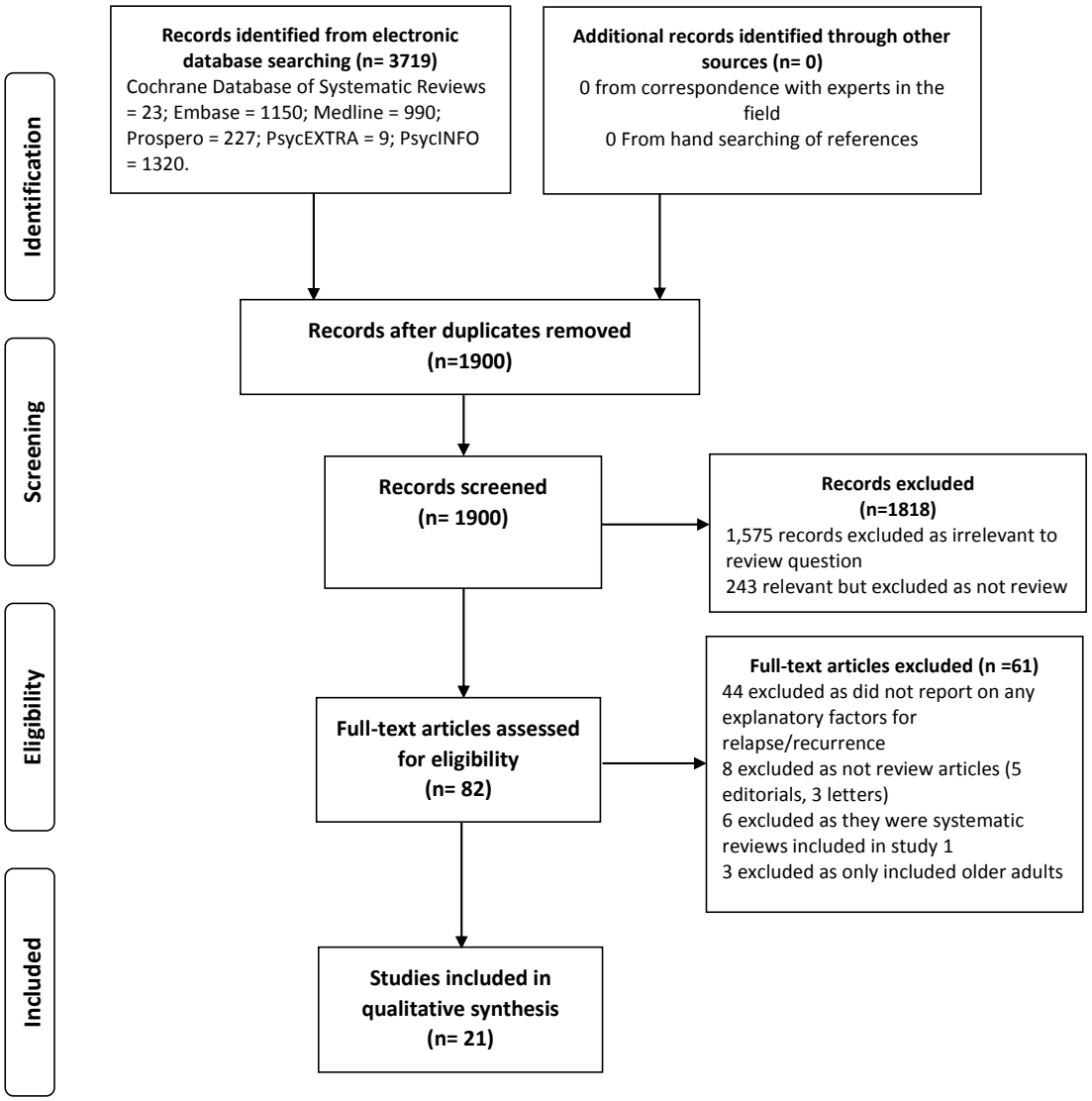
From each included study data relevant to the methods used to identify studies (where given), the main results of relevance to relapse/recurrence and any proposed mechanisms to explain relapse/recurrence to depression were extracted by a single reviewer. These data were then used to build a matrix as in Study 1. Given the low quality of these studies, any evidence relating to factors identified in the matrix in Study 1 was excluded from the present study matrix as the evidence for these came from higher quality reviews and is therefore considered more robust. Quality ratings were not made for these reviews, as being non-systematic there are no established criteria for judging their quality and as they do not report any specific methods for conducting the review it is reasonable to assume that against any existing quality rating criteria they would all be judged as of 'very low quality'.

Results

Twenty one non-systematic reviews identified as meeting inclusion criteria from the bibliographic database searches were included in the present study (see Figure 2). The studies reviewed in each included non-systematic review were cross-checked with those reviewed in the systematic reviews in Study 1 to ensure that they were able to contribute knowledge beyond the findings of Study 1. Of the 702 studies included in all 28 reviews, only 22 were reviewed by reviews included in both Study 1 and Study 2. None of the 21 non-systematic reviews included more than two articles also reviewed by Study 1 reviews.

Figure 2.

Flow diagram of study selection.



Characteristics of the included studies

Given the narrative nature of most non-systematic reviews it is difficult to determine what exactly has been included in the review and therefore extracting data on the study type, population, interventions, comparisons, and outcomes of relevance to the present review was not always possible. Where multiple study designs were cited in a review this has been reflected in the study characteristics table (Table 5). However where a review cited mostly one type of study design but supplemented it with mention of one or two different types of study, the predominant design of the cited studies has been outlined in the table. All of the included studies reviewed clinical trials, cohort studies, experimental studies, or neuroimaging studies, with 11 of the 21 including more than one type of study. Several of the included studies also reviewed case-control studies, cross-sectional studies, quasi-experimental studies, and/or animal laboratory studies.

Many of the included studies focussed or reported on factors suggested as related to relapse in Study 1, with seven studies reporting positive associations between cognitive biases and relapse, seven reporting on the relationship between stressful life events and relapse, and five studies reporting a positive association between ruminative thinking patterns and relapse. However, a number of factors not identified in Study 1 were also reported to be associated with relapse. In particular, eight studies reported associations between relapse and information processing biases, and six studies reported a positive association with relapse and either dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, dysregulation of rapid eye movement (REM) phase sleep, or both.

Matrix of factors associated/not associated with relapse and proposed mechanisms of action

Details of the factors reported to be associated or not associated with relapse in each of the included studies along with any proposed mechanism of action can be found in Table 6. Overall, the reviewed studies propose associations between the presence of information

processing biases, cognitive biases, and rumination and greater risk of relapse. Each study reporting on these factors considers slightly different mechanisms of action, though there are some common themes among them: the suggestion that such biases are triggered in response to a change in mood (to become dysphoric); that there is a learned association between the depressed state and the biases, as they occur together; and the biases may trigger ruminative patterns of thinking by increasing awareness of negatively valenced information and decreasing awareness of positively valenced information, impacting upon the ability to recognise positive social cues and privileging depressogenic attributions. Such processes might then lead to further engagement in depressive thinking patterns, then might lead to greater depressive symptoms, and eventually to relapse/recurrence. These processes are proposed to be accentuated by limbic and neocortical reactivity to changes in mood, in particular by dysregulation of the HPA axis which may act as a long-term diathesis for depression onset if occurring early in the life-course, and REM sleep dysregulation which interrupts the ability to process emotionally valenced information and to regulate affect.

Table 5.

Data extracted from included non-systematic reviews.

Reviewed Studies	Study design of included studies	Study population and Intervention	Comparisons	Results of relevance to relapse/recurrence
Beckerman & Corbett, 2010	Clinical trials	Adults with depression or formerly depressed. Treated with MBCT, MBSR, CT, TAU or ADM	Between treatment groups	Thought processing and poor attentional control may be related to depressive relapse.
Belsher & Costello, 1988	Cohort studies	Adults	Relapsers vs non-relapsers	The longer patients stay well, the less likely they are to relapse. Factors increasing risk of relapse are: recent environmental stress, absence of social support from family members, a history of depressive episodes, persistent neuroendocrine dysregulation. No significant associations between gender, marital status, or socioeconomic status and relapse.
Burcusa & Iacono, 2007	Cohorts, cross-sectional studies and clinical trials	children, adolescents, students, adults, and older adults	Recurrence vs non-recurrence, between groups of those with different treatment(s)	Gender, SES, and marital status are not risk factors for recurrence. Age at onset, number of prior episodes, severity of the first or index episode, comorbid psychopathology especially other affective disorders, and family history of psychopathology, particularly depression or other affective disorders, all associated with increased risk of recurrence. Negative cognitions, high neuroticism, poor social support, and stressful life events may be risk factors for recurrence.
Costa e Silva, 2004	Neuroimaging studies, clinical trials, and animal studies	Adults with depression treated with ADM; animals used to test ADM	Depressed vs healthy controls, and between treatment groups relapsers Vs non-relapsers	Alteration of metabolism and atrophy and/or death of specific neural populations, in brain structures involved in the control of mood and emotions; the hippocampus, the amygdala, and prefrontal cortex, resulting in a decrease in neuroplasticity, may be in the etiology of depression. The decreased risk of relapse with maintenance anti-depressant medication may be related to alterations in neuroplasticity.
de Carvalho Tofoli et al., 2011	Neuroimaging studies, experimental studies, quasi-experimental studies, cohort studies, and animal studies	Adults with depression treated with ADM, adults under influence of stressors	Relapsers Vs Non-relapsers	Dysregulation of the HPA axis is partially attributable to an imbalance between GRs (glucocorticoid receptors) and MRs (mineralocorticoid receptors). Evidence has consistently demonstrated that GR function is impaired in major depression, resulting in reduced GR-mediated negative feedback on the HPA axis.
Hammen, 2003	Cohort studies	Adults with Depression; recovered depression; recurrent depression	Relapsers vs non-relapsers	Negative interpersonal events brought about by stress generation may increase risk of relapse in women.
Hick & Chan, 2010	Clinical trials	Adults with recurrent depression	Relapsers vs non-relapsers	Cognitive reactivity to sad mood is associated with depressive relapse following successful treatment. Rumination predicts the severity, duration, and recurrence of depressive symptoms. Several studies reported that rumination prolongs and intensifies depression by enhancing the effects of depressed mood on negative thinking.

Hollon & DeRubeis, 2009	Clinical trials	Mostly adults with depression	Relapsers vs non-relapsers	Explanatory style represents an example of the kind of depth cognitions likely to be involved relapse episodes. Explanatory style also predicted relapse after controlling for treatment type, and is suggested as a mediator of the effect of treatment on risk of relapse.
Keller, 1996	Cohort studies	All ages of people with depression treated with ADMs	Relapsers vs non-relapsers	Most important predictor of recurrence is number of previous episodes. No other factors showed an association with risk of relapse without first controlling for the number of previous episodes. Probability of relapse within 6 months rose to 95% for those with 3 or more previous depressive episodes. Other risk factors were: double depression, onset after the age of 60, long duration of individual episodes, family history of affective disorder, comorbid anxiety disorder or substance abuse, and poor symptom control during continuation therapy. This latter factor is particularly important, becoming wholly symptom-free had a profound effect on risk of relapse.
Kerr et al., 2013	Neuroimaging studies and clinical trials	mostly adults with depression, some with recurrent depression	Relapsers vs non-relapsers	The effect of Mindfulness practice on reducing the risk of depressive relapse may function as it enhances attentional control, possibly by acting upon the prefrontal cortical areas known to regulate the thalamocortical circuits.
Kessler, 1997	Cohort studies and case-control studies	Adults with depression; adults vulnerable to depression due to stress; healthy adults	Depressed vs non-depressed	Young age at first onset associated with recurrence. Childhood adversity is associated with increased risk of onset before 20 years old. Few of the childhood adversity factors continue to be associated with risk of recurrence. There is no difference in risk of recurrence by gender.
Lau, Segal & Williams, 2004	Experimental and quasi-experimental studies	Formerly depressed adults	Formerly depressed compared to never depressed adults	Increased accessibility and activation of negative thinking patterns induced by sad mood were associated with increased risk of relapse.
Liu, 2013	Cohort studies, retrospective case-control studies, experimental studies, quasi-experimental studies, cross-sectional studies	Adults with depression, adults under influence of stressors	Depressed vs healthy controls	Genetic factors are suggested to moderate the relationship between behavioural risk factors and relapse to depression. Stress generation is tentatively proposed to provide the mechanism for this, but the evidence for this was weak.
Modell & Lauer, 2007	Neuroimaging studies, genetic sequencing studies, and animal studies	adults with depression treated with Sleep Deprivation	Depressed vs healthy or at risk controls	Dysregulated REM sleep was suggested to be associated with an increased risk of relapse risk.
Monroe & Harkness, 2005	Cohort studies, retrospective case-control studies, experimental studies, cross-sectional studies	Mostly adults with depression but also adolescents	Relapsers vs non-relapsers	The stress sensitization and stress autonomy models provide very different accounts of the basic finding that life stress is more important for a first lifetime episode of depression than for a later recurrence. The stress sensitization model appears to provide the more parsimonious account of the existing data. Nonetheless, the stress autonomy model provides an important conceptual alternative. The authors suggest both models play important roles in helping understand relapse.

Palagini,Baglioni, Ciapparelli, Germignani & Reimann, 2013	Neuroimaging studies	adults with depression treated with Sleep Deprivation	Depressed adults, vulnerable adults, formerly depressed, vs healthy controls.	REM sleep alterations, particularly shortened REM latency are proposed as risk factors for relapse.
Robinson & Sahakian, 2008	Experimental and neuroimaging studies	Adults treated for depression or vulnerable to depression, and healthy controls	Depressed, vulnerable to depression, vs healthy controls	The authors report that: rumination, negative biases, memory problems and cortisol release all increase with successive episodes but sleep efficacy and social interaction ability diminish. Kindling may explain why first episodes are triggered by stressful life events and subsequent episodes can be triggered by lower levels of stress.
Scher, Ingram & Segal, 2005	Experimental studies	Children, adolescents, students, and adults - never depressed or formerly depressed	non-depressed, formerly depressed, remitted, vs recovered depressed. Within groups comparing vulnerability over time.	The one study to directly investigate cognitive reactivity as a predictor of relapse found that it increases the risk of relapse. This supports the proposal that processes such as attention and interpretive biases play an important role in relapse.
Scott, 2001	Clinical trials	Adults with depression	Between treatment groups	Patients with residual depressive symptoms were found to have a 50–80% risk elapse. CT reduced risk of relapse by changing thinking style not thought content in particular reducing absolutist, dichotomous thinking.
Segal et al., 1996	Experimental studies	Mostly adults with depression/formerly depressed	Depressed, formerly depressed vs never depressed	Depression-related information processing (mediated by cognitive reactivity) may lead to other depressogenic processes increasing the risk of relapse.
Sipe & Eisendrath, 2012	Neuroimaging studies, clinical trials, and experimental studies	Adults with depression/recurrent depression	Relapsers vs non-relapsers	Rumination, particularly brooding on past failures and anxiety (future-based ruminations) are associated with the course of depression. In Mayberg's model depression is characterized by higher baseline amygdala activity, higher amygdala reactivity to emotional stimuli, and dysfunction between limbic and cortical circuits that regulate affective states.

Abbreviations: ADM – antidepressant medication; CT – cognitive therapy; DAH – differential activation hypothesis; DAS – dysfunctional attitude scale; GRs - glucocorticoid receptors; HPA – hypothalamo-pituitary-adrenal; MBCT- mindfulness based cognitive therapy; MBSR – mindfulness based stress reduction; MRs - mineralocorticoid receptors; REM – rapid eye movement; SES – socio-economic status; ST – standard; TAU – treatment as usual.

Table 6.

Factors associated and not associated with relapse/recurrence to depression in adults reported in each of the included non-systematic reviews, and proposed mechanisms of action.

Study Citation	Factors investigated for their association with relapse/recurrence								Proposed mechanisms of action
	Stressful Life Events	Neuroendocrine or HPA Axis Dysregulation	Sleep Dysregulation	Cognitive Reactivity	Information Processing Biases	Cognitive Biases	Rumination	Other	
Beckerman & Corbett, 2010					++	++			Depressive relapse may be due to faulty thought processing and attentional control.
Belsher & Costello, 1988	++	++						Duration of wellness after last episode ==	None stated
Burcusa & Iacono, 2007	++								None stated
Costa e Silva, 2004								Decreased Neuroplasticity ++	Alteration of metabolism or atrophy in neural structures involved in the control of mood and emotions may play a key role in the etiology of depression.
de Carvalho Tofoli et al., 2011		++							Early life stress leads to permanent changes in the HPA axis and may lead to the development of depression in adulthood
Hammen, 2003	++								Maladaptive cognitions about attachment and dysfunctional interpersonal skills contribute to the stress generation and hence relapse.
Hick & Chan, 2010				++			+		Small change of mood to one that is dysphoric may trigger negative attitudes, thinking patterns and beliefs, and these may be underlined by rumination. When this happens negative feelings worsen and intensify and magnify negative thoughts and feelings. This may generate even more overwhelming negative thoughts and negative attitudes setting off a depressive relapse.

Hollon & DeRubeis, 2009				+	++		Hopelessness =	Change in readily accessible beliefs and expectations may mediate the reduction of acute distress, whereas change in underlying information-processing may play a larger role with respect to the prevention of relapse.
Keller, 1996							Double depression ++ Poor symptom control during continuation phase treatment +	None stated
Kerr et al., 2013	+			++	+	++		Body-focused attentional practice enhances localized attentional control, thought to play a key role in regulating sensory input to sensory neocortex and in enhancing signal-to-noise properties across the neocortex, thus acting against the information processing biases apparent in depressed and formerly depressed individuals which otherwise negatively impact on their ability to utilise social interactions and support and therefore increase their risk of relapse.
Kessler, 1997							Younger age ++; Demographics = =	Inventories of stressful events predict subsequent depression. partly due to events causing depression but the reverse is also true. The association between stressful life events and depression is moderated by prior characteristics of the people exposed to the events and the environments in which these people are embedded.
Lau et al., 2004			++	++	++			Cognitive reactivity is an independent predictor of depressive relapse; increased negative cognition(s) manifest during induced sad mood or a naturally occurring mild depressed mood are predictive of depressive relapse/recurrence.
Liu, 2013	++						5-HTTLPR genotype interacting with relational attachment security +	Dependent stress may interact with the underlying depressogenic vulnerability that produces it, thereby elevating risk for depression beyond what may be accounted for by either variable alone.
Modell & Lauer, 2007		++						None stated

Monroe & Harkness, 2005	++						The stress sensitization model predicts that life events meeting minimal criteria for triggering recurrence are even more common given stress generation. In contrast, for the stress autonomy model, stress generation would have less powerful implications over time, given the proposed uncorrelated eventual relationship between life stress and recurrence.
Palagini et al., 2013		++					REM sleep may help regulate affective reactivity and emotional information processing in depression. Stress-related REM sleep hyperactivation/disinhibition could affect adult neurogenesis and thus might endanger hippocampal integrity, thereby contributing to the development of mood disorders through allostatic load.
Robinson & Sahakian, 2008	+	+		+	+		Different symptoms of depression involve different patterns of neural activation that become associated during a first episode and that this could underlie the 'kindling' effect.
Scher et al., 2005			++	++			Cognitive vulnerability may contribute to depression relapse and that vulnerability may originate in part from interactions that occur within the context of childhood attachment relationships.
Scott, 2001				+	++	Extreme Response Style (on self-report questionnaires) ++	The way depressed patients process depression related material, rather than the content of their thoughts may be critical in preventing relapse.
Segal et al., 1996				++			Once activated, depression-related patterns of processing may lead to behavioural processes which in turn increase risk of relapse.
Sipe & Eisendrath, 2012		+			+	High amygdala reactivity and dysfunction in cortico-limbic circuits +	Catastrophic ruminations and threat avoidance may be accompanied by limbic dysfunction. Mindfulness may interrupt the cycle of rumination about past regrets or future fears, and enhance self-compassion, breaking the link between cognitive reactivity and escalating depressive symptoms.

Key: ++ good evidence of positive association with relapse; + some evidence/suggestion of positive association with relapse; = = good evidence of no association with relapse; = some evidence/suggestion of no association with relapse

Abbreviations: CT – cognitive therapy; HPA – hypothalamo-pituitary-adrenal; REM – rapid eye movement; SSRI – selective serotonin reuptake inhibitor; ST – standard.

Discussion

From the twenty-one included non-systematic reviews there is some continuity with what was found in Study 1, with the addition of other variables and proposed mechanisms of action that may be helpful to consider for the consulting clinician. The matrix from the included reviews points to a role for cognitive processing and information processing biases, perhaps triggering ruminative thinking in the context of experiencing some change in mood, perhaps due to stressful life events. These factors were suggested to be associated with greater reactivity in the neocortical and limbic pathways and dysregulation of the HPA axis and REM sleep. However, given that the reviews were non-systematic and therefore of very low quality (although the quality of the studies reviewed therein may have been of reasonable quality but this was not reported on), the factors proposed to affect risk for relapse and their proposed mechanisms of action must be treated with great caution.

Recently a number of researchers have reconceptualised models of depression to consider relationships such as those noted above between various cognitive and information processing biases and the onset of depressive symptoms (e.g. Disner, Beevers, Haigh & Beck, 2011; Roiser et al., 2012). The 'cognitive neuropsychological' model of depression (e.g. Roiser et al., 2012) proposes that negative affective biases result in changes in monoamine transmission, giving rise to negative belief systems that subsequently result in the signature features of a depressive episode: anhedonia and dysphoria (Roiser et al., 2012). Such biases rely on both 'bottom-up processes' (as they may be triggered by emotionally salient stimuli, such as stressful life events), and 'top-down processes' (as cognitive mechanisms which are needed to inhibit reactions to emotionally salient but task-irrelevant information are known to function sub-optimally in depressed patients) (Castaneda et al., 2008; Clark et al., 2009b; Fales et al., 2008; Roiser et al., 2012). These authors have also suggested that evidence for the mechanisms proposed in the

'cognitive neuropsychological model' of depression will be best delivered by neuroimaging studies and/or studies utilising an experimental paradigm to manipulate mood, cognitive processing or information processing (Roiser et al., 2012).

Study 3

Aim

The present study aims to systematically review neuroimaging and experimental studies to investigate any further factors proposed to be associated with relapse to depression in adults and the mechanisms of action for such factors.

Methods

A systematic review of experimental and neuroimaging studies was conducted in accordance with the preferred reporting items for systematic reviews (PRISMA) guidelines wherever possible (Moher et al., 2009).

Search Strategy

Studies were identified using a combination of keyword and subject heading searches on: CAB Global Health Archive 1910 to 1972, Cochrane CENTRAL Trial Register (searched on 16th November 2013), Embase 1947 to 2013 Week 47, International Pharmaceutical Abstracts 1970 to November 2013, Ovid MEDLINE 1946 to November Week 3 2013, PsycEXTRA 1908 to November 16, 2013, and PsycINFO 1806 to November Week 3 2013. Each database was searched individually and results were combined before removing duplicates. Search terms included variations of phrases such as "depression" or "major depression" or "major depressive episode" or "MDD" or "unipolar depression" or "depressive episode", and "relapse" or "recurrence", and "risk" or "explanatory factor". A full list of all the searches conducted and results thereof can be found in Appendix II.

Study Selection

All search results were reviewed by a single reviewer using the same process as for Study 1. Hand searching of references from studies included in Studies 1 and 2 as well as the present study was then conducted in order to identify further studies for this review.

Inclusion Criteria*:* Studies were included if: 1) they were neuroimaging or experimental studies; 2) they provided data on at least one explanatory factor for relapse/recurrence to depression; 3) they had some longitudinal measurement of depressive symptoms over a minimum of eight weeks and either a clinical interview to determine status of onset, remission, recovery, relapse, and/or recurrence, or used a well validated interviewer-rated or self-report measure(s) of depressive symptoms, or they made a cross-sectional comparison between groups of remitted and relapsed/recurrently depressed participants determined by diagnosis from a psychiatrist or with a clinical interview; 4) they included adults over the age of 18 years old; and 5) they were journal articles published in the English language.

Exclusion Criteria: Studies were excluded if: 1) they were not neuroimaging or experimental studies; 2) they provided no data on any explanatory factors associated with relapse/recurrence to depression; 3) they were studies of populations with bipolar disorder, psychotic depression, seasonal affective disorder, depression secondary to organic brain disorders, or those focussing on relapse to other conditions (such as drug or alcohol misuse disorders) comorbid to depression; 4) they were studies of children or adolescents (i.e. those younger than 18 years old), including studies of the impact of parental depression on children, or studies of older adults only, and/or factors relevant only to a geriatric population; 5) they were not journal articles; and 6) they were not published in the English language.

Data extraction and quality ratings

Data were extracted from each included study by a single reviewer, on information relevant to the methods of participant recruitment; inclusion and exclusion criteria; how depressive status and/or symptoms were determined at baseline; the participants; and experimental interventions and/or means of neuroimaging. In addition, the comparisons drawn between or within groups of participants; the outcomes reported and the means by which these were recorded; and the main results of relevance to factors associated with relapse and any proposed mechanism(s) of action, were extracted by a single reviewer. Quality ratings for all included studies were established independently by two reviewers, with disputes resolved by consensus or by consultation with a third reviewer where necessary.

Study quality was assessed with criteria proposed by Kmet et al. (2004), using a 14-item rating scale where each item is a question about how the study was conducted and/or reported, e.g. 'Design evident and appropriate to answer study question?'. Each item has four possible responses 'yes', 'partial', 'no', or 'n/a'; items are given a score of two if the answer is 'yes', one if the answer is 'partial', and zero if the answer is either 'no' or 'N/A'. A summary score is then calculated by summing the score from the 14 items and dividing it by 28 minus the number of not-applicable items multiplied by two, to derive a total score of between zero and one. No grading of study quality is suggested by the authors (Kmet et al., 2004) so the GRADE categories (Guyatt et al., 2008) were used as discussed above (Study 1). The following was used to guide judgements of overall study quality: studies scoring between 0 and 0.25 were considered to be of very low quality; studies scoring between 0.26 and 0.50 as low quality; studies scoring between 0.51 and 0.75, or studies scoring above 0.75 but scoring 0 on the sample size item or not scoring 2 on items related to using appropriate outcome measures, conducting appropriate analyses, and being able to support conclusions with the data, were considered as moderate quality; and if the

above criteria were met and the studies scored 0.76 or above they were considered as high quality.

Information extracted on factors proposed to be associated or not associated with relapse to depression, along with any proposed mechanisms of action, was used to build a matrix such that every proposed factor could be considered from the perspective of each included study. The strength of association between the factor and relapse/recurrence reported in each study was considered and entered into each cell of the matrix as in Studies 1 and 2 above.

Results

A total of 15 studies were found to meet inclusion criteria and were included in the present review (see Figure 3 for a flow diagram of study selection).

Characteristics of the included studies

Eleven of the 15 studies utilised experimental paradigms to manipulate cognitive processing, information processing, mood, or a combination thereof. One study included some neuroimaging, two were targeted neuroimaging studies with an experimental task, and two were quasi-experimental studies with laboratory-based measurements of cognitive processing or information processing but with no experimental manipulation (e.g. Risch et al., 2010 used an Implicit Association Test to measure the association between implicit self-esteem and recurrent depressive episodes though did not manipulate self-esteem).

Study Quality

Seven of the included studies were judged to be of high quality (see Table 8) (Dai & Feng, 2011; Franck, De Raedt, & De Houwer, 2007; Lethbridge & Allen, 2008; Morris, Rao & Garber, 2012; Nixon, Liddle, Worwood, Liotti & Nixon, 2013; O'Brien-Simpson, Di Parsia, Simmons & Allen, 2009; Segal et al., 2006), a further seven were judged to be of moderate

quality (Anderson et al., 2011; Chopra, Segal, Buis, Kennedy, & Levitan, 2008; Huffziger & Kuehner, 2009; Risch, et al., 2010; Sears, Newman, Ference & Thomas, 2011; Segal, Gemar & Williams, 1999; Watkins & Baracaia, 2002), and one study was judged as low quality (Moreno, George, Heninger, McGahuey & Delgado, 2000). The high quality studies focussed on a range of factors associated with relapse, with three of the seven (Dai & Feng, 2011; Lethbridge & Allen, 2008; Nixon et al., 2013) considering cognitive biases (including rumination), information processing biases/affective biases, or some combination thereof, whereas six of the seven moderate quality studies reported on these factors (the exception being the study by Risch et al., 2010). The one low quality study focussed on manipulating mood with tryptophan depletion and reported on the relationship between dealing with a change in mood for the worse and relapse (Moreno et al., 2000).

Figure 3.

Flow diagram of study selection.

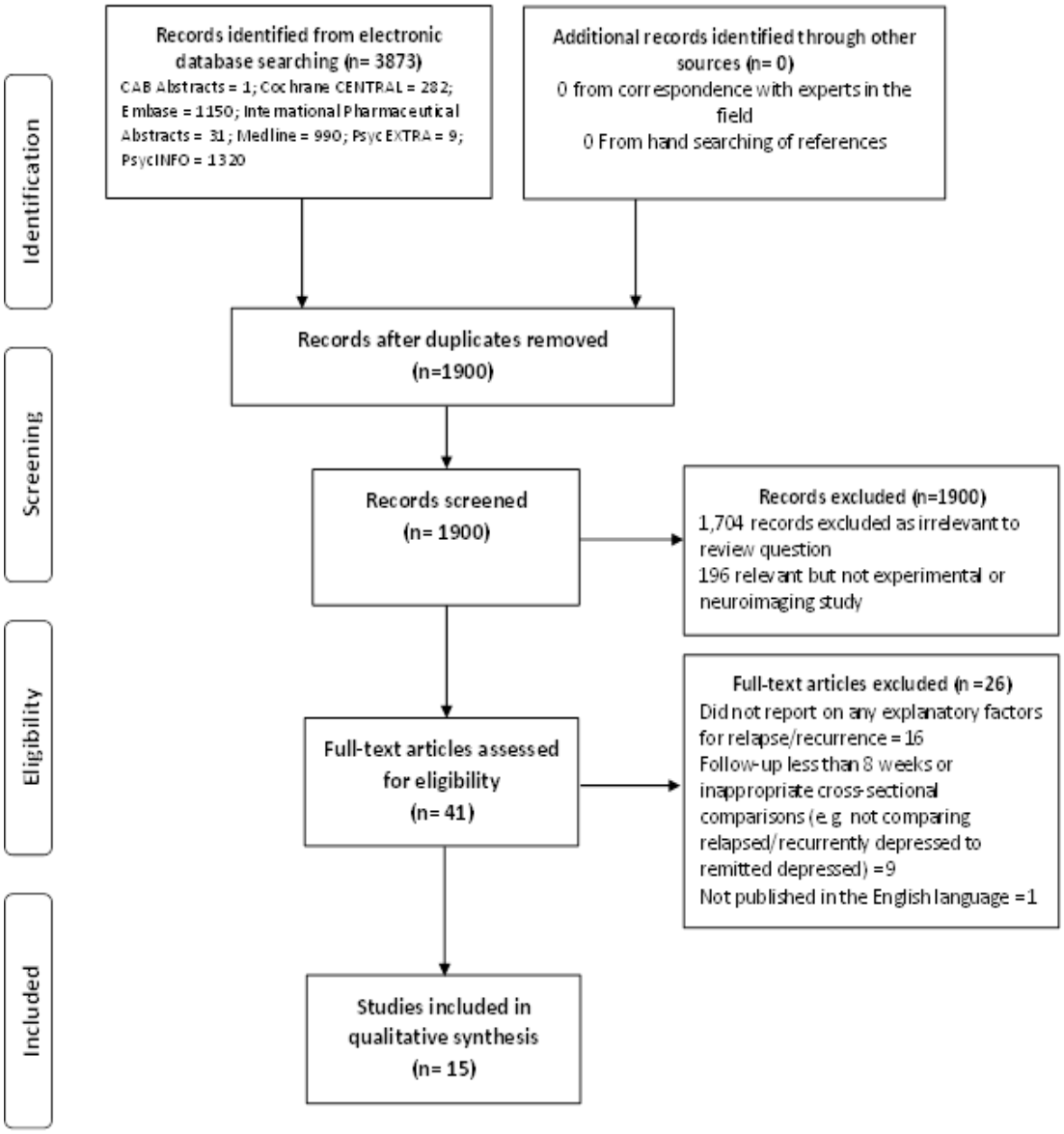


Table 7.

Characteristics of included experimental and neuroimaging studies.

Reviewed Studies	How Depression Determined at Baseline	Population Characteristics	Intervention details including method of delivery and setting	Comparisons and Ns	Outcomes and How Recorded	Results of relevance to relapse/recurrence
Anderson et al., 2011	SCID, MADRS, and the Clinical Anxiety Scale (CAS) derived from the Hamilton Anxiety Scale.	N= 230. Current Depressed mean age 38.6(10.9) mean 6.3(4.4) previous episodes, 53% on ADM; Remitted group mean age 34.2(10.8) 3.0(2.2) previous episodes, 17% on ADM; Controls age 30.3(10.1). 159 female.	Face Emotion Recognition Task. Participants are asked to correctly recognise expressions of anger, disgust, fear, happiness, sadness and surprise with intensities of 30, 50, and 70%, and neutral expression.	Healthy Controls N= 101, Current Depressed N= 30, Remitted Depressed N= 99	The number of correct items recognised, false positives, and reaction times for each item were recorded.	Remitted group correctly identified a more emotions than did controls and those currently depressed. Participants with current depression had impaired accuracy owing to decreased discrimination as to whether an emotion was present. The effect was mainly driven by the negative emotions anger, fear and sadness.
Chopra et al., 2008	HRSD and BDI	N= 55 (35 female), mean age 38.8(10.1). 37 patients had 3 or more past depressions.	Listened to ''Russia under the Mongolian Yoke'', while recalling a sad time in their lives.	Relapsers (28) Vs Non-Relapsers (27).	Salivary cortisol samples taken at -25, 0, +25, +45 and +65 minutes relative to mood induction. Change in DAS score to assess relationship between cognitive reactivity and relapse.	Dysfunctional attitudes in response to mood induction predicted relapse. Participants with three or more episodes were more likely to relapse. For patients with high cortisol at 25 min rates of relapse were equivalent regardless of past depression history. For patients with low cortisol at 25 min those with no/fewer past episodes of depression had lower rate of relapse.
Dai & Feng, 2011	SCID, HRSD, and BDI	Groups were age and sex matched; mean ages: Normal Controls: 25.71(3.72); Remitted depressed: 27.53(6.36); MDD: 27.59(3.74). 60% of MDD group were outpatients with no comorbid disorders. 6 of MDD and 3 RMD taking ADM.	Stroop Colour Word task - 50 positive, neutral and negative words. Ignore meaning respond to colour. Brain EEG activity, HEOG and VEOG tracked.	MDD (N=17), RMD (N=17), NC (N=17)	Word accuracy, false positive rate, reaction time, ERPs and EEG latencies.	MDD participants showed deficient behavioural and neurophysiological indices of attentional inhibition for negative words. This impaired inhibition of negative information was accompanied by reduced N1 amplitude and enhanced N450 component in these trials.
Franck et al., 2007	MINI interview based on DSM-IV criteria, HRSD and BDI-II-NL.	Mean ages Never Depressed (ND) 45.3(7.3) 8 males, Formerly Depressed (FD)43.8(9.4) 3 males, Currently Depressed (CD) 39.6(12.1) 10 males.	Participants were asked to rate how beautiful they found each letter of the alphabet.	CD (N=28), FD (N=34), ND (N=33)	BDI at baseline for all three groups and 6 months follow-up for ND and FD only. RSES at baseline only.	CD patients had lower explicit self-esteem compared to FD and ND controls. After controlling for initial symptoms of depression higher levels of implicit self-esteem were associated with higher levels of depressive symptomatology at follow-up.

Huffziger & Kuehner, 2009	SCID-I and MADRS	Mean ages: Rumination group 51.37(11.82) 50% female, Distraction 45.95(12.96) 52% female, Mindful self-focus 44.85(10.38) 48% female. Groups did not differ on baseline variables all ps> .10.	Sad mood induction with negative autobiographic recall. Randomly assigned to one of three groups (rumination, distraction, or mindful self-focus).	58 remitted patients, 5 with residual symptoms and 13 with current MDD. Compared across induction groups - Rumination (n=24) Distraction (n=27) and Mindfulness (n=25).	Response styles measured with RSQ. Habitual aspects of mindfulness using FMI-14 and mood using PANAS.	Controlling for baseline MADRS, there were differences between induced rumination and both mindfulness and distraction groups. Habitual distractive coping predicted less negative and more positive mood. Habitual mindfulness enhanced improvement of negative mood specifically after mindful self-focus.
Lethbridge & Allen, 2008	SCID, BDI, Visual Analogue Scale, DAS	20 males, 32 females, mean age 32.7(11.7). Mean number of previous episodes 1.94(range 1-6). Mean age of onset 24.42(10.25).	Mood induction consisted of autobiographical recall of depressing experience followed by mood-congruent music.	48 of 52 completed follow up. 17 Relapsed (14 once, 3 twice) over the 12 months.	BDI, SCID, if relapsed then life events questionnaire was also used.	Changes in happy mood following a mood induction were associated with increased risk for relapse. Changes in depressed mood following a sad mood induction and changes in dysfunctional thinking did not predict relapse.
Moreno et al., 2000	HAM-D	N=12 all with history of MDE but in remission, and 12 age- and gender-matched controls with no personal or family history of any mental disorder.	Two TRP depletion tests, separated by 1 week. One full-strength and one quarter-strength. Double-blind, crossover design.	MDE over follow-up (N=9 from the 24 participants) compared to no-MDE during follow-up (N=15).	Behavioural ratings obtained at baseline and 5, 7 and 28 hours after depletion. HAM-D was completed weekly for 1 month, and then monthly for 3 months. Retrospective HAM-D and SCID at 6 and 12 months.	An increase of 5 or more in HAM-D score during depletion predicted relapse. Relapse was not associated with age, gender, type of past treatment, length of remission, or number of past MDEs.
Morris et al., 2012	SCID-I and BDI-II	N= 68, 32 remitted depressed (RD), and 36 never depressed (ND), mean age =23.39(3.88); 43 were female (63%).	Randomly assigned to high stress or low-stress condition. Cortisol measured after a 10min rest, after a 10min preparation period, after the reading task, and the arithmetic task, after 10mins rest and another 10mins rest.	RD vs ND	Trier Social Stress Test and salivary cortisol. LIFE administered each week during follow-up. The Perceived Events Scale was used to measure number and severity of stressful life events during follow-up.	Individuals with high-anticipatory stress cortisol and more MDEs were at significantly greater risk of recurrence compared to individuals with low-anticipatory stress cortisol and fewer MDEs. Individuals who showed higher cortisol reactivity to a relatively low-level stressor were at greater risk of experiencing subsequent depressive symptoms.
Nixon et al., 2013	SCID & HAM-D	Controls (n=20) mean age 43(24-63), 30% male, and Patients (n=20) mean age 45(25-63), 35% male.	In fMRI Scanner after baseline images two 10-min trials of a Go/No-Go task with visual negative feedback were administered.	Unmedicated patients, medicated patients, and controls. Also compared recurrers (n=7) to non-recurrers (n=11).	SCID conducted at 4-montly intervals for 1-year, clinical data gathered from case-notes. Accuracy of responses to task measured.	Hypoactivity in BA 9 of the right dmPFC, believed to play a role in affective regulation was found in patients but not in controls. Some processing of negative experiences at this site may have a protective effect against depression as the dmPFC inhibits ventral, limbic regions allowing for adaptive reappraisal of negative stimuli.

O'Brien-Simpson et al., 2009	SCID and BDI	33 participants assessed in remission from depression, 25 followed-up (19 female, 6 male; age range 20 to 63 years) 2 years later. 9 Ps were on ADM. Duration of remission prior to testing ranged from 73 to 3820 days; Mean= 697 days (SD 903).	Startle probes were bursts of white noise at 100 dB. Startle reflex was measured by surface EMGs. Participants were assessed 1–2 weeks apart. Each time performing an affective picture viewing task, with startle probes. Participants induced to euthymic mood once and depressed mood once.	Relapsers (n=7) Vs Non-relapsers (n=18), and participants that experienced residual depressive symptoms over the follow-up period (n=19) vs those that did not (n=6).	SCID, LIFE used to track symptoms weekly over 2 years and to take monthly measures of social support.	Baseline startle magnitude predicted depressive symptoms and recurrence over the follow-up. Number of past episodes also predicted outcome.
Risch et al., 2010	SCID and BDI	Currently Depressed (N=24): 13 females, mean age 40.2(12.1); Recurrently Depressed (N=28):19 females, mean age 50.1(10.9); Remitted Depressed (N=33) : 20 females, mean age 40.1(13.1); Never Depressed (N=34): 20 females, mean age 44.6(12.7).	Implicit Association Test. Participants were asked to categorise words as fast as possible combined with a self-positive and a self-negative task. Following the IAT completed the BDI and DAS.	First-onset currently depressed patients vs recurrently depressed vs remitted depressed patients vs never depressed	DAS and IAT	No significant correlation between implicit self-esteem and the number of depressive episodes. First onset CD and RCD patients did not significantly differ in implicit self-esteem.
Sears et al., 2011	BDI, PANAS and a developed self-report measure based on DSM-IV-TR criteria for MDE.	Never Depressed (ND): N=38, Mean age 20.7(3.4), Previously Depressed (PD): N=15, Mean age 21.3(4.1), Dysphoric (DY): N=24, Mean age.	160 colour images: depression-related, anxiety-related, positive, and neutral. Eye movements were recorded. Recognition memory test with the 160 images and 160 new images. Asked to choose: sure old, guess old, sure new, or guess new.	ND vs PD vs DY	Type of image initially fixated on in each trial, number and duration of fixations to each image type measured in milliseconds. Signal detection measure d-prime, used for recognition memory accuracy.	PD and DY participants attended to positive images less than ND participants and PD attended to anxiety-related images more than ND or DY. PD and DY had poorer recognition memory than ND. There was no interaction between group and image type.
Segal et al., 1999	RDC. Remission confirmed by SADS-L interview, HRSD and BDI scores. VAS and DAS also used.	CBT Group (N=25): Mean age 40.5(10.7), 10 males, mean previous episodes 6(10.0); PT Group (N=29), Mean age 39.7(8.0), 12 males, mean previous episodes 3.6(2.1).	Completed VAS then modified Stroop task and then listened to Russia Under the Mongolian Yoke with sad autobiographical recall for 10mins.VAS again after completing Stroop Task.	Remitted depressed CBT Vs PT. Pre induction vs post induction. Relapsers (N=14) compared to non-relapsers (N=16).	DAS. Relapse using SCID and BDI. Only 30 agreed to take part in the follow up, 10 CBT, 20 PT.	The PT group showed a greater increase in cognitive reactivity compared against the CBT group. DAS at time of testing predicted relapse status for 75% of those that did not relapse, and 64.4% of those that did. Changes in DAS after mood induction increases risk of relapse.

Segal et al., 2006	SCID pre-treatment, LIFE and HDRS post-treatment. Completed a DAS and VAS pre-post induction and BDI-II prior to mood-induction.	ADM (N=40), mean age 39.65(11.49), 23 females, 14 first episode, mean previous episodes 1.65(0.48), mean HDRS score 5.23(2.77), mean DAS pre mood-induction 134.73(28.09). CBT group: (N=59) mean age 38.17(10.95), 36 females, 13 first episode, mean previous episodes 1.71(0.46), mean HDRS 5.29(2.80), mean DAS pre mood-induction 128.17(30.04).	ADM condition: treated first-line antidepressant medications for 6 months. CBT condition: 20 individual weekly sessions of CBT. Mood induction using 'Russia under the Mongolian Yoke' played at half speed and recalling a time in their life that made them sad.	99 participants induction and entered an 18-month clinical follow-up. Main comparison was relapsers (n=42) vs non-relapsers (n=57).	Patients completed BDI-II and HDRS-17 bimonthly for 18 months post mood-induction. If consistently in depressed range given LIFE. Judged to have relapsed if they were given a diagnosis of MDE at any time during the follow-up. Other outcome measures were DAS and VAS.	After controlling for history of depression cognitive reactivity is a meaningful predictor of relapse irrespective of previous treatment modality. Each 16 point increase of the DAS following mood-induction increased the risk of relapse by 42%. Patients with marked increases in cognitive reactivity had higher relapse rates (69%) than those with minimal increases in cognitive reactivity (30%) or with marked decreases in cognitive reactivity (32%).
Watkins & Baracaia, 2002	SCID and BDI	Currently Depressed N=32: mean age 42.3(12.8), 24 females. 81.2% on ADM, current episode length mean 8.7(9.2) months, age at first onset 21.5(8.3), mean previous episodes 6.2(3.4). Recovered Depressed N=26: Mean age 41.8(9.9), 18 females. 15.4% currently on ADM, mean age of first onset 27.6(12.9) and mean previous episodes 3.1(2.6). Never Depressed N=26: mean age 36.1(12.2), 16 females, none currently on ADM.	Randomly allocated to the conditions (no questions, n=27; state-oriented, n=29; process focused, n=28). Participants were presented with scenarios and asked to think of best solution to each one. They were presented with extra material based on their allocated condition.	Within-groups comparisons were made based on condition. Between groups: Currently Depressed (N=32), Recovered Depressed (N=26) and Never Depressed (N=26).	BDI, Mood measure rating mood 0 (I do not feel at all despondent) to 100 (I feel extremely despondent). RRS measuring how often one responds to a sad mood with rumination. The Means-Ends Problem-Solving Test (MEPS) measuring ability to conceptualise step-by-step means of achieving a goal.	Within the no question condition: The currently depressed group produced significantly less effective solutions than the recovered depressed and never depressed groups. In the state-oriented condition: Both the currently depressed and recovered depressed groups produced significantly fewer relevant means and less effective solutions than the never depressed group. Within the process-focussed condition: there was no effect of group. The currently depressed group were more despondent than the recovered depressed and never depressed groups.

Abbreviations: ADM – antidepressant medication; ANOVA – analysis of variance; BA – Brodmann's area; BAI – Beck Anxiety Inventory; BDI/BDI-II/BDI-II-NL – Beck Depression Inventory; CAS – clinical anxiety scale; CBT - cognitive behaviour therapy; CD – currently depressed; CH – correct hit; CI – confidence interval; CSI –chronic somatic illness; DAS – Dysfunctional attitude scale; db – decibel; df – degrees of freedom; dmPFC – dorsal medial pre-frontal cortex; DP – double button press; DSM-IV/DSM-III – Diagnostic and Statistical Manual of Mental Disorders 4th/3rd Edition; EC – error commission; EEG – electroencephalography; EMG – electromyography; ERP – event related potentials; FD – formerly depressed; FMI-14 Freiburg Mindfulness Inventory; HAM-D – Hamilton depression rating scale; HEOG – horizontal electrooculography; HRSD - Hamilton rating scale for depression; IAT – implicit association test; ICD-10 – International Classification of Diseases 10th Edition; LIFE – Longitudinal interval follow-up evaluation; MADRS – Montgomery-Asberg Depression Rating Scale; MBCT –Mindfulness based cognitive therapy; MDD – major depressive disorder; MDE – major depressive episode; MEPS – Means ends problem solving test; ms – millisecond; NC – never disordered controls; ND – never depressed; NLPT - RCT – randomised controlled trial; PANAS – Positive and Negative Affect Schedule; PSR – psychiatric status rating; PT – pharmacotherapy; rACC – right anterior cingulate cortex; RCD – recurrently depressed; RDC – research diagnostic criteria; RMD – remitted depressed; RRS – Ruminative response scale; RSES- Rosenberg Self-Esteem Scale; RSQ - Response Styles Questionnaire; SADS-L – schedule for affective disorders and schizophrenia lifetime version; SCID – Structured Clinical Interview for DSM-IV; SD – standard deviation; TRP – tryptophan; VAS – visual analogue scale; VEOG – vertical electrooculography; VNF - visual negative feedback.

Table 8.
Rating of study quality for included studies using criteria from Kmet et al. (2011).

Study Citation	Question/objective sufficiently described?	Study design evident and appropriate?	Method of group selection described and appropriate?	Subject (and comparison group) characteristics sufficiently described?	Random allocation procedure described?	Blinding of investigators reported?	Blinding of subjects reported?	Outcome and exposure	Sample size appropriate?	Analytic methods justified and appropriate?	Estimate of variance reported for the main results?	Controlled for confounding?	Results reported in sufficient detail?	Conclusions supported by the results?	Total Score	Maximum Possible score: 28-(No of N/A Items x2)	Total Score / Maximum Possible Score	*Proposed Quality Category*
Anderson et al., 2011	1	2	2	2	N/A	N/A	N/A	2	1	1	0	0	2	1	14	22	0.64	Moderate
Chopra et al., 2008	1	2	1	1	N/A	N/A	N/A	2	1	2	0	2	2	2	16	22	0.73	Moderate
Dai & Feng, 2011	2	2	1	2	N/A	2	N/A	2	1	2	0	1	2	2	19	24	0.79	High
Franck et al., 2007	2	2	2	2	N/A	N/A	N/A	2	1	2	0	0	2	2	17	22	0.77	High
Huffziger & Kuehner, 2009	2	2	1	2	2	0	0	2	1	2	0	0	2	2	18	28	0.64	Moderate
Lethbridge & Allen, 2008	2	2	1	2	N/A	N/A	N/A	2	1	2	1	2	2	2	19	22	0.86	High
Moreno et al., 2000	0	1	0	1	1	0	0	1	1	1	0	0	1	2	9	28	0.32	Low
Morris et al., 2012	2	2	1	2	1	0	0	2	1	2	2	2	2	2	21	28	0.75	Moderate
Nixon et al., 2013	2	2	2	2	N/A	N/A	N/A	2	1	2	2	1	2	2	20	22	0.91	High
O'Brien-Simpson et al., 2009	2	2	1	2	N/A	N/A	N/A	2	1	2	0	2	2	2	18	22	0.82	High
Risch et al., 2010	2	2	1	2	N/A	N/A	N/A	2	1	2	0	0	2	2	16	22	0.73	Moderate
Sears et al., 2011	2	2	1	1	N/A	N/A	N/A	1	1	2	0	0	1	2	13	22	0.59	Moderate
Segal et al., 1999	2	2	1	2	N/A	N/A	N/A	2	1	2	0	0	2	2	16	22	0.73	Moderate
Segal et al., 2006	2	2	2	2	1	0	0	2	2	2	1	2	2	2	22	28	0.79	High
Watkins & Baracaia, 2002	2	2	1	2	1	1	0	2	1	2	0	1	2	2	19	28	0.68	Moderate

Table 9.

Factors associated and not associated with relapse/recurrence to depression in adults reported in each of the included experimental and neuroimaging studies, and proposed mechanisms of action.

Study citation and quality rating	Factors investigated for association with relapse/recurrence to depression								Proposed mechanisms of action
	Stressful Life Events	Neuroendocrine /HPA Axis Dysregulation	Cognitive Reactivity	Information Processing Biases	Cognitive Biases	Rumination	Self-Esteem	Other	
Anderson et al., 2011 Moderate				++					Depression is associated with abnormalities in face emotion recognition which differ according to current mood state. The increased bias to recognise emotions in remitted depression is a possible mechanism of susceptibility to depression, although the effect was small
Chopra et al., 2008 Moderate		++	+		++				Combination of high cortisol and three or more prior episodes increased risk of relapse. Cortisol and cognitive predictors of relapse were not associated with each other; they might represent separate vulnerabilities to relapse.
Dai & Feng, 2011 High				++					MDD and RMD participants showed deficient attentional inhibition of negative material.
Franck et al., 2007 High							(++ Implicit) (- - Explicit)	Severity of last episode ++	A higher implicit self-esteem reveals a vulnerability for depression
Huffziger & Kuehner, 2009 Moderate						++			Induced rumination maintained rather than exacerbated negative affect. Rumination may both prolong and exacerbate periods of negative mood.
Lethbridge & Allen, 2008 High	++		++					Dysfunctional thinking =	Change in dysfunctional thinking following sad mood induction did not emerge as a causal risk factor for depressive relapse. However, affective reactivity to the mood induction, specifically the degree of reduction in happy mood, emerged as an independent predictor of relapse. Finally, life stress was also a strong and significant predictor of relapse.

Moreno et al., 2000, Low			++					Double depression, duration of wellness after last episode and demographics, all = =	How a formerly depressed patient responds to a change in mood for the worse can determine whether or not they will relapse.
Morris et al., 2012, High	+	++							Individual differences in HPA function during remission may serve as an indicator of vulnerability to recurrent depression.
Nixon et al., 2013, High	+			++	++			Hypoactivity in right dmPFC and right ACC ++	The importance of dmPFC and rACC processing within the time-frame utilised in the present study may lie in early, adaptive reappraisal of negative experiences, and a failure to do this may lead to vulnerability to depressive relapse.
O'Brien-Simpson et al., 2009 High								Attenuated startle response ++	Inhibited baseline startle may be a reliable endophenotypic marker of biological predisposition to recurrent depression
Risch et al., 2010 Moderate							++ (Implicit)		None stated
Sears et al., 2011 Moderate				++					Information processing biases are not transient symptoms of depression but are instead an important vulnerability factor.
Segal et al., 1999 Moderate			++		++				None stated
Segal et al., 2006 High			++						A mild negative mood experienced by someone with a history of depression, can trigger some of the cognitive features of a depressed episode. The presence of such reactivity in recovered patients signals a residual but heightened risk for relapse.
Watkins & Baracaia, 2002 Moderate	+		+	++		++		Psychosocial impairment post MDE ++	One possible mechanism of relapse in recovered depressed patients is state-oriented ruminative responses to a stressful life event leading to impaired social problem solving and further escalation of the stressful situation.

Key: ++ good evidence of positive association with relapse; + some evidence/suggestion of positive association with relapse
= = good evidence of no association with relapse; = some evidence/suggestion of no association with relapse
- - good evidence of negative association with relapse; - some evidence/suggestion of no association with relapse

Matrix of factors associated/not associated with relapse

Several factors were endorsed as positively associated with relapse/recurrence for which there was good evidence from high quality experimental or neuroimaging studies. The three studies rated as high quality and the six studies rated as moderate quality to investigate cognitive biases or information processing biases all suggested a positive association between the presence of such biases and the risk for relapse. There was also good evidence for cognitive reactivity as a risk factor for relapse from two high, three moderate, and one low quality study. The precise role of stress was not clear from the studies, although four of the studies reported positive associations between experiencing stress and relapse. One high quality and one moderate quality study reported good evidence of a positive association between HPA axis dysregulation and relapse, though the latter reported that this was only the case for those patients that had a history of three or more previous depressive episodes. The neuroimaging studies reported good evidence for dysregulation and/or morphological alterations in areas related to emotional and information processing and relapse, in particular hypoactivity in neocortical and limbic areas (particularly the dmPFC and rACC) induced by a stimulus (Nixon et al., 2013) and reduced hippocampal volume measured in a resting state (Kronmuller et al., 2008).

There were few concretely proposed mechanisms of action from the included studies, though there were some consistencies in the tentative proposals made and two of the studies (Nixon et al., 2013; Segal et al., 2006) were somewhat more definitive. Overall, the studies proposed a role for dysfunction in neural networks responsible for information processing or affective and cognitive processing in response to either stress/anticipation of stress (which may be influenced by dysfunction in the HPA axis) or a change in mood, which prevents appropriate reappraisal of negative experiences. When accompanied by ruminative thinking styles, this prolongs the negative mood state and prevents the patient

from recognising and utilising social cues and social support, and thus confers greater risk for relapse.

Discussion

From the 15 included studies there was some consistency with the results of Studies 1 and 2; cognitive biases including rumination and information processing biases (also referred to as affective biases) were found to be associated with greater risk for relapse, as were dysfunction in the HPA axis, incurring stressful life events, and greater reactivity to a negative change in mood. In addition, the studies reviewed provided evidence for hypoactivity and morphological alterations in neocortical and limbic regions underlying the above biases and impacting upon the ability to manage stress or changes in mood.

The matrix from the included studies also supports the mechanisms proposed in Study 2: providing greater evidence for the assertion that in formerly depressed patients there is greater risk of relapse/recurrence when the neural networks responsible for information processing and cognitive processing dysfunction in response to stress (which may also be influenced by dysfunction in the HPA axis) or a change in mood (particularly from a positive to neutral mood), thus preventing appropriate reappraisal of negative experiences. The suggestion is that this can trigger rumination about the negative experiences, thus maintaining the resulting negative mood and preventing the patient from finding solutions to their problems or from recognising and utilising social cues and social support. Taken together these factors are proposed to lead to a greater likelihood of relapse to depression.

General Discussion

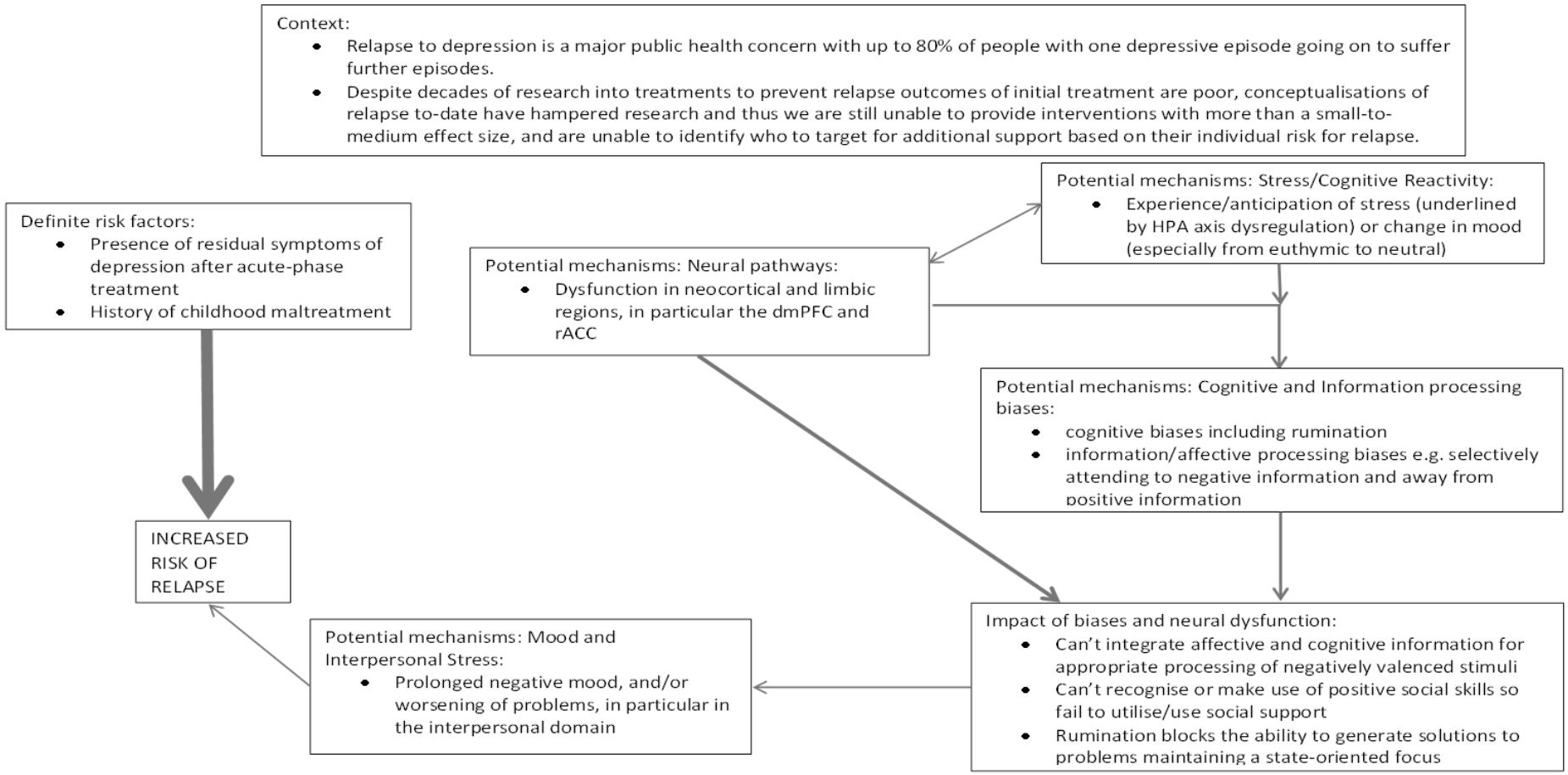
Study 1 demonstrated that only the presence of residual sub-syndromal symptoms after acute phase treatment and the experience of some form of maltreatment during childhood are well supported as risk factors for relapse to depression. There were other factors

potentially linked to relapse but without good evidence to support them. Study 2 highlighted several other factors as potentially linked to relapse, such as information processing and cognitive biases, ruminative thinking, and HPA axis and REM sleep dysregulation. However, the studies reviewed were of very low quality by virtue of being non-systematic and so these potential associations were not able to be considered as valid. Study 3 systematically reviewed experimental and neuroimaging studies based on the suggestion by Roiser and colleagues (2012) that such study designs are needed in order to provide evidence for components proposed in the 'cognitive neuropsychological' model of depression (e.g. Roiser et al., 2012). The study showed that there is evidence for the associations between the biases proposed in Study 2 and relapse to depression, and that these biases are associated with dysregulation at the neural level.

Studies 2 and 3 also investigated mechanisms proposed by authors of the reviewed studies to consider the nature of the relationships between the factors identified as conferring risk for relapse and the outcome (relapse/recurrence) itself. These have been used to develop the conceptual framework shown in Figure 4.

The conceptual framework points to a need for studies of interventions targeting any or all of the following in order to reduce the risk of relapse: cognitive reactivity or stress reactivity; cognitive and information processing biases; and dysfunction in the HPA axis and neocortical and limbic regions. Further, trials of relapse prevention interventions should ensure patients have a complete absence of depressive symptoms before ending treatment, wherever possible. Clinicians may also want to consider the role of any childhood maltreatment suffered by their patients in formulating their depression and planning any relapse prevention interventions.

Figure 4.
Conceptual Framework for Studying Relapse to Depression.



Limitations

There are several limitations to the present studies. Study 1 was hampered by a paucity of systematic reviews of risk factors of relapse to depression, and in particular systematic reviews that had a stated aim to identify/consider the relative strength of multiple risk factors for relapse. The three included systematic reviews that did attempt to do this were all of low or very low quality and so the results from these studies were necessarily treated with caution. However, the study was nonetheless able to support the consensus view (Campbell, 2009) with regard to residual symptoms, and question it with regard to the number of previous episodes, and further, was able to add to the consensus view with the finding of an additional risk factor – childhood maltreatment.

Both Studies 1 and 2 were limited by a lack of reporting on the quality of the studies reviewed therein. While the quality of the reviews was judged, it may be the case that some of the lower quality reviews included high quality studies and therefore the findings from these may have effectively been 'downgraded' by the quality criteria being applied at the level of the review and not at the level of the included studies. Further, the reviews included in Studies 1 and 2 did not include a number of studies that may have been relevant to the present review. As a part of the systematic review process, a large number of cohort studies, RCTs and case control studies (128 studies) were identified that reported on risk factors for relapse/recurrence but these studies were not included in the reviews which made up Studies 1 and 2. This may be a consequence of the aims of the included reviews, which as noted were generally not focussed on specifically identifying risk factors for relapse to depression, but instead focussed on treatment efficacy of relapse prevention interventions and reported on factors identified as associated with relapse as secondary aims. What is more, it is by no means guaranteed that the results of Studies 1 and 2 would have been altered if RCT and cohort studies were included.

Most studies that have sought to identify risk factors for depressive relapse have been hampered by methodological weaknesses and inconsistencies (Burcusa & Iacono, 2007). For example, many of the longitudinal studies have used hospital readmission rates to determine relapse/recurrence and thus introduced selection bias as this may only account for the most severe of cases, those with greatest access to healthcare/greatest healthcare utilisation, or those most likely to be treated as inpatients (Hatch et al., 2011; Hatch & Thornicroft, 2012). Furthermore, many of the RCTs have required participants to be free of comorbid mental health problems, but this may not be representative of the clinical population (Kessler et al., 1996; 2007), and in addition many of the RCTs and cohort studies (in particular the long-term large scale cohort studies) have suffered from high drop-out/loss-to-follow-up therefore introducing further bias in the interpretation of their results (Burcusa & Iacono, 2007).

Another potential limitation arose in the use of categorical statements of study quality in Studies 1 and 3. Neither the AMSTAR (Shea et al., 2007) nor criteria developed by Kmet et al. (2004) include guidance on making statements about the overall quality of reviewed studies. However, in order to bring a common framework to the present article as a whole, it was decided that using the categories proposed by Guyatt and colleagues (2008) in the GRADE system would be most appropriate. Further, it was important to not only use the outcomes from the AMSTAR or Kmet quality rating criteria but to add to these considerations from other best available quality rating systems/statements such as PRISMA (Moher et al., 2009) and the Cochrane Reviewer's Handbook (Higgins & Green, 2008). As such the present review suggested quality ratings for articles reviewed in Studies 1 and 3 but these were used only to guide considerations about the validity of the results from each included study and not to concretely weight the degree of evidence as is commonly done in a quantitative synthesis.

Further limitations were apparent as six articles across Studies 1, 2 and 3 were excluded after reading the abstracts (despite being considered as relevant) as they were not published in the English language. There was no budget for a translation of these studies so it may be that they would have contributed further to our understanding of relapse/recurrence. In addition, the reviewed studies primarily used the Frank et al. (1991) definitions of relapse and recurrence, but which may have led to a degree of bias in the results as they tend to compare people who do not relapse over the study period with people that do relapse without separating out those that have had multiple previous episodes and those that have had their first lifetime episode, thus potentially under-sampling those that only ever have a single lifetime episode (Monroe & Harkness, 2011).

Finally, despite the knowledge of cognitive and information processing biases having been discussed in the literature for quite some time, there appears to be little utilisation of it in the consulting room. Further when it is utilised it has not significantly improved relapse prevention interventions as none of these have greater than a small-to-medium effect size in preventing relapse (Clarke et al., in press). It may be that depression as a category and/or relapse/recurrence as a singular construct, might be better represented by novel nosological systems seeking to define disorders by clusters of behavioural and/or functional experiences and underlying biology, rather than by the presence of a certain number of a group of diffuse symptoms (Cuthbert & Insel, 2010; Insel et al., 2010). As such, it may not be possible to significantly improve existing interventions for relapse prevention until such a time as these novel nosological systems are in place.

Conclusion

Taken together these three studies have demonstrated that: 1) the current consensus view of relapse is not entirely supported by the evidence base and needs amending; 2) there are no factors that are supported by studies able to provide the strongest level of evidence for the prognosis or aetiology of a disease conducted with high quality and which have utility in

guiding the treating clinician in reducing their patient's risk of relapse/recurrence to depression; and 3) there are, however, a number of factors which to date had not previously been systematically reviewed that these studies suggest play a role in conferring risk for relapse. These are information processing and cognitive biases, reactions to stress and/or changes in mood, and persistent ruminative thinking in response to negative experiences that may be targeted in psychological interventions aimed at preventing relapses/recurrences. Further, the three studies have identified several potential mechanisms for the action of such risk factors and have considered the inter-relationships between these factors to propose a conceptual framework that may help guide future research into relapse/recurrence to depression. On the basis of this we might hypothesise that research investigating the causal pathways between either childhood maltreatment or acute-phase treatment outcomes for depressed patients, and dysfunction in the neocortical and limbic pathways that control processing of affective information and/or cognitive control, might shed greater light on the associations linking the factors identified herein. In addition, the conceptual framework points to a need for studies of interventions targeting the identified mechanisms, for trials of relapse prevention interventions to ensure patients have an absence of depressive symptoms before ending treatment, and for clinicians to consider the role of childhood maltreatment in their formulations with patients, particularly when planning any relapse prevention stage of treatment. Knowledge from studies accounting for these factors might allow the treating clinician to target their interventions at mechanisms operating at the level of the individual, which may help improve their patient's chances of prolonging a period without relapse to depression or avoiding it altogether. However, implicit in this is that the concept of depression as a single disorder is valid. Newer nosological sysytems based on functional experiences and/or underlying biology may change this view. One advantage of taking the approach in the current article is

that the conceptual framework may also contribute to the knowledgebase of relapse to depression if and when such systems come in to common use.

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PART 2: EMPIRICAL PAPER

Can we learn more about relapse to depression by understanding patient trajectories throughout treatment and beyond? A study of patients treated in primary care mental health services.

Abstract

Aims: To analyse data from service users of a primary care mental health service to identify risk factors for the presence of residual symptoms of depression post-treatment and for relapse, and to determine what factors impact the rate of relapse. A prospective study was used to investigate the relationship between cognitive control and depressive symptoms. **Method:** Logistic regression models were built comparing 54 relapsers to non-relapsers (n=13,072), and comparing those with residual symptoms (n=11,515) to those without (n=9,709). Kaplan-Meier plots were used to compare survival based on factors identified in the multivariable regression models. Cox proportional hazards models were built to consider the multivariable effects of factors in the model on the hazard rate of relapse. An algorithm developed by Saunders et al. (submitted) was used to determine the distribution of service users across eight latent profiles based on factors measured pre-treatment. For the prospective study a sample of 64 service users treated for depression at 'Step 2' were recruited and cognitive control was measured at every treatment session. **Results:** Residual symptoms were an important predictor of relapse to depression and of relapsing more quickly as was attending ten or more sessions. For those with a GAD-7 score recorded this was the strongest predictor of relapse. High GAD-7 scores, attending fewer than ten sessions, not completing treatment and being in receipt of benefits were all risk factors for relapsing more quickly. The latent profiles of those that relapsed was different from non-relapsers and those that remained recovered though not from those that had residual symptoms at the end of treatment or those that stayed depressed throughout treatment and beyond. Cognitive control was able to predict the presence of residual symptoms of depression. **Conclusions:** Cognitive control can be used to predict levels of depressive symptoms post-treatment in a clinical setting. However, relapse was not measured prospectively in conjunction with cognitive control and so the exact nature of the relationship between these factors is yet to be determined.

Introduction

Depression is one of the most common mental health problems worldwide, causing significant impairments in social functioning, having an adverse effect on physical health, increasing the risk of mortality from all causes, in particular from suicide, and therefore resulting in a heavy burden for sufferers and health services alike (Murray & Lopez, 1996; Prince et al., 2007). Long-term prospective studies have reported that up to 80% of those with depression will relapse at least once (Judd, 1997; Kessler & Wang, 2009; Mueller et al., 1999; Murray & Lopez, 1996; Roiser, Elliot & Sahakian, 2012), with an average of approximately four episodes per sufferer, each lasting approximately 20 weeks (Judd, 1997). Therefore, it is of great importance that treatments for depression are not only successful at relieving symptoms so service users can recover from the index episode, but that they are also successful in reducing the risk of relapse to further episodes (Teasdale et al., 2000).

Treatment for Depression in Primary Care Services

The majority of service users in the UK presenting for psychological treatment for depression are seen in primary care services (Cape, Whittington, Buszewicz, Wallace, & Underwood, 2010). In England and Wales treatment follows a stepped-care model based on the National Institute for Health and Clinical Excellence (NICE) Guidelines for Depression (NICE, 2010). The majority of service users are seen in Improving Access to Psychological Therapies (IAPT) services where approximately two thirds of patients are treated at 'Step 2', which for the most part involves once-weekly 30-minute sessions of guided self-help interventions based on cognitive behavioural therapy (CBT) and behavioural activation (Dimidjian et al., 2006). For those attending at least two of these 'Step 2' intervention sessions 55-56% recover from their depressive episode (Clark et al., 2009a; Richards & Suckling, 2009). However, there is no routine follow-up after treatment in IAPT services so

very little is known about those that relapse into depression, the risk and protective factors for relapse, and the rate at which relapse occurs following treatment (Clark et al., 2009a).

The Current State of Knowledge on Relapse

The majority of studies of relapse to depression focus on specific sub-groups of the population receiving treatment, for example by excluding those with comorbid mental health problems or only including those that are deemed able to make use of a particular type of therapy (Burcusa & Iacono, 2009). In these studies populations tend to be drawn from secondary care centres or involve convenience sampling, thus either being unrepresentative of the whole population of depressed patients or introducing a high risk of selection bias. This therefore makes it difficult to interpret findings of such studies for the large population of those presenting to health services with significant depressive symptoms. In addition, early studies of relapse to depression used different definitions of relapse making it difficult to compare results across studies (Monroe & Harkness, 2011). Although most researchers now follow the definition of relapse proposed by Frank and colleagues (1991), it has recently been suggested that further biases may have been introduced by researchers not separating out those that have suffered a first life-time episode of depression from those that have suffered multiple previous episodes (Monroe & Harkness, 2011). In so doing such studies potentially lead to spurious conclusions about the risk and protective factors for relapse and the course of depression by combining results from those that have and have not already suffered past relapses (Buckman, Fearon & Pilling, submitted; Monroe & Harkness, 2011).

The current consensus view of relapse to depression is that only the presence of residual symptoms post-treatment and having a history of two or more depressive episodes prior to the index episode are significant predictors of relapse (Campbell, 2009). However, a recent systematic review suggests that this latter factor may not be a reliable predictor of relapse to depression, although maltreatment during childhood is considered

to be an important risk factor (Buckman et al., submitted). This review highlighted a number of affective and information processing biases that have been proposed to have significant roles in relapse to depression, though they have not been studied sufficiently to make firm conclusions about their relationships with relapse (Buckman et al., submitted). Given the paucity of factors identified to reliably predict relapse to depression, it is not surprising that clinicians cannot accurately predict who will relapse following treatment or when relapses are most likely to occur (Beckerman & Corbett, 2010; Buckman et al., submitted; Hughes & Cohen, 2009; Roiser, et al., 2012). It is also unsurprising therefore that there are no relapse-prevention treatments with more than a small-to-medium effect size for preventing relapse (Clarke, Mayo-Wilson, Kenny, & Pilling, in press).

The Cognitive Neuropsychological Model of Depression

In an attempt to better understand the nature of depression some recent studies have sought to explain the course of depression from a neuropsychological perspective. The 'cognitive neuropsychological' model of depression (e.g. Roiser et al., 2012) proposes that the negative affective biases commonly demonstrated in depressed patients (such as selectively attending to negatively valenced information and selectively ignoring positively valenced information) are present to a lesser degree prior to an episode of depression (Roiser et al., 2012). These negative affective biases are thought to result in changes in monoamine transmission giving rise to negative belief systems/schemata which subsequently result in the signature features of a depressive episode: dysphoria and anhedonia (Clark, Chamberlain, & Sahakian, 2009b; Pringle, Browning, Cowen, & Harmer, 2010; Robinson & Sahakian, 2008; Roiser et al., 2012). Further, this model proposes that the negative affective biases rely on both 'bottom-up processes' as they may be triggered by emotionally salient stimuli, such as stressful life events, and 'top-down processes' as cognitive mechanisms which are needed to inhibit reactions to emotionally salient but task-irrelevant information are known to function sub-optimally in depressed patients

(Castaneda et al., 2008; Clark et al., 2009b; Fales et al., 2008; Roiser et al., 2012). Experimental and neuroimaging studies have demonstrated that depressed patients exhibit deficits in the construct posited to underlie this top-down process: cognitive control (Castaneda et al., 2008; Channon, Baker, & Robertson, 1993; Desseilles et al., 2009; Elliot et al., 1996; Fales et al., 2008; Siegle, Thompson, Carter, Steinhauer, & Thase, 2007).

Cognitive Control

Cognitive control includes functions such as being able to selectively attend to certain information whilst ignoring distractions, being able to wilfully and quickly engage or disengage attention from a given stimulus, and being able to remember and mentally manipulate information (after it has stopped being presented/disappeared). It is noteworthy that patients who have recovered from a depressed episode have been observed to exhibit impaired cognitive control (Smith, Muir, & Blackwood, 2006), and as such it may be that impaired cognitive control is related to the presence of residual symptoms in formerly depressed patients, the risk factor most reliably associated with relapse (Buckman et al., submitted; Campbell, 2009). However, to date there have been no studies known to this author of the relationship between depressive symptoms and cognitive control in clinical settings, and no longitudinal studies investigating cognitive control and either residual depressive symptoms or relapse to depression. Therefore the nature of the relationships between cognitive control, residual symptoms of depression post-treatment, and relapse to depression are yet to be understood.

Research Questions and Hypotheses

If cognitive control underlies the negative affective biases that are fundamental to causing depressive episodes, then it may be hypothesised that those with a greater degree of cognitive control post-treatment would be less likely to relapse than those with a lesser degree of cognitive control post-treatment. This may or may not be mediated by the

presence of residual symptoms of depression post-treatment. Therefore, if it were possible to determine the degree of cognitive control that each patient exhibits at the start and end of their IAPT treatment, it may be possible to identify those at greatest risk of relapse.

Aims

The present study therefore aims to:

1) Analyse data in a dataset from an inner London Trust's IAPT services based on information gathered pre, during and post-treatment to determine and predict the trajectory of patients through their contact with these services, in order to understand more about who finishes treatment with residual symptoms of depression, who relapses, when relapses occur and what confers risk for relapsing and for relapsing more quickly.
2) To determine whether the IAPT treatment for depression affects levels of cognitive control, whether there is a relationship between any reported changes in cognitive control and changes in depressive symptomology, and to consider the relationship between cognitive control and residual symptoms of depression at the end of treatment.

Methods

Overview

The IAPT Services Dataset: All patients seen in IAPT services across England and Wales give information regarding their demographics, such as age, gender, and ethnicity, at their first contact with the services. They then complete self-report measures of symptoms of depression and anxiety, along with other information related to work and social functioning and any other relevant symptomology, at every contact with the services (Clark et al., 2009a; IAPT, 2011). The inner London Trust's IAPT services have been operating since 2007 and the data collected from patients seen in these services from that time until the

present are held anonymously in a database and are used to evaluate the services' performance against various nationally determined targets and against other IAPT services nation-wide (e.g. Clark et al., 2009a; IAPT, 2012). Over the course of the last five years a number of service users seen in these IAPT services have returned for further treatment, some of whom have relapsed to depression. In the current study, these relapsers are compared to those that did not return to the IAPT services having relapsed to depression, to form a naturalistic retrospective cohort study to meet aim 1 above.

Prospective Study: To meet aim 2 (above) all service users starting treatment for depression at 'Step 2' within the inner London Trust's IAPT services between September 2013 and April 2014 were asked for consent to participate in a prospective study.

Design

The present study is based on two linked but separate sub-studies, as they are linked the results and discussion are presented together as one overall study. The first sub-study consists of a secondary data analysis of a large database of service users referred to the IAPT services, some of whom returned to the service thus forming a naturalistic retrospective cohort study. The second is a prospective cohort study of service users receiving 'Step 2' interventions for depression.

Participants

For the database analysis, only service users meeting criteria for caseness on the Patient Health Questionnaire (PHQ-9) (Kroenke, Spitzer, & Williams, 2001) at the start of their treatment were included in the analyses. For analyses specifically relating to relapsers to depression, additional inclusion criteria were: 1) scoring below the criteria for caseness on the PHQ-9 at the point of discharge from the IAPT services; and 2) subsequently experiencing a clinically significant increase in score on the PHQ-9 from the time of discharge to the time of return to the services.

For the prospective study Psychological Wellbeing Practitioners (PWPs) working within the IAPT services sought consent from all service users engaged in 'Step 2' interventions for depression that met criteria for caseness on the PHQ-9 and had a working diagnosis of depression.

Measures

The data contained in the IAPT database consists of scores on a range of routine measures used in all IAPT services. At every contact with the IAPT services clients are asked to complete a PHQ-9 (Kroenke et al., 2001), a Generalized Anxiety Disorder scale (GAD-7) (Spitzer, Kroenke, Williams, & Lowe, 2006) the IAPT phobias scale (IAPT, 2011), and the Work and Social Adjustment Scale (W&SAS) (Mundt, Marks, Shear & Greist, 2002).

The PHQ-9 (Kroenke et al., 2001) is a nine item measure of depressive symptoms designed for use with primary care patients. Respondents are asked to rate how bothered they have been by a list of symptoms, such as "Little interest or pleasure in doing things" over the past two weeks, on a scale of zero ("Not at all") to three ("Nearly every day"). The cut-off for caseness is suggested as a score of 10 such that scoring 10 or above indicates clinically significant self-reported symptoms of depression (Kroenke et al., 2001).

The GAD-7 (Spitzer et al., 2006) is a seven item measure of general anxiety symptoms and has utility in identifying those with other common anxiety disorders such as panic disorder, social anxiety disorder, and post-traumatic stress disorder (IAPT, 2011). The GAD-7 uses the same format and scale as the PHQ-9. Items include symptoms such as "Feeling nervous, anxious or on edge". The cut-off for caseness is a score of eight or above indicative of clinically significant symptoms of generalised anxiety.

The IAPT Phobias scale (IAPT, 2011) is used to identify those with significant levels of anxiety that may be missed by the GAD-7, for example those with agoraphobia or a specific phobia. Respondents are asked to rate how much they would avoid each of three situations on a scale from zero ("would not avoid it") to eight ("always avoid it"). The three

items are: “Social situations due to a fear of being embarrassed or making a fool of myself”; “Certain situations because of a fear of having a panic attack or other distressing symptoms (such as loss of bladder control, vomiting or dizziness)”; and “Certain situations because of a fear of particular objects or activities (such as animals, heights, seeing blood, being in confined spaces, driving or flying)”. This scale is not validated as a screening instrument, however there is a suggested cut-off of a score of four or more on any of the three items indicating significant levels of phobic anxiety (IAPT, 2011).

The W&SAS (Mundt et al., 2002) is a five-item measure of the impact of mental health problems on functioning: (1) at work; (2) in the home; in leisure activities (both (3) social and (4) private); and in (5) family relationships. Respondents are asked to rate the degree of problems they have with each of the five areas on a scale of zero (“not at all”) to eight (“very severely”). A cut-off score of 20 has been suggested to indicate significant difficulties in functioning (Mundt et al., 2002).

Additional measures used in prospective study only: Participants in the prospective study completed the Attentional Control Scale (ACS) (Derryberry & Reed, 2002), and the Beck Depression Inventory (BDI-II; Beck et al., 1996). The BDI-II was used as it is deemed to be more sensitive to depressive symptomology than the PHQ-9 and therefore better able to inform the analyses of the relationship between cognitive control and depressive symptoms.

The ACS is a 20-item self-report measure asking participants to rate how frequently they experience the phenomenon presented in each question on a four-point scale from “almost never” to “always”. The ACS includes items related to focussing attention (e.g. “My concentration is good even if there is music in the room around me”), shifting attention (e.g. “After being distracted or interrupted, I can easily shift my attention back to what I was doing”), and flexible control of thinking (e.g. “I can become interested in a new topic very quickly if I need to”). Higher scores indicate less resistance to interference, greater

ability to disengage from threat-related stimuli, and greater activation of neural areas related to top-down emotion regulation (Gyurak & Ayduk, 2007; Mathews, Yiend, & Lawrence, 2004).

The BDI-II (Beck et al., 1996) is a 21-item measure of depressive symptomology with respondents asked to rate how they have been feeling in relation to each item over the last two weeks on a scale of zero to three, for example: 'Sadness: 0 "I do not feel sad.", 1 "I feel sad much of the time", 2 "I am sad all the time", 3 "I am so sad or unhappy that I can't stand it"'. Higher overall scores represent greater severity of depressive symptomology. The conventionally used cut-offs for the BDI-II are as follows: scores between 0-13 are deemed representative of 'minimal' levels of depression; scores between 14-19 are indicative of 'mild' levels of depression; scores between 20-28 are indicative of 'moderate' levels of depression; and scores between 29-63 indicate 'severe' levels of depression (Beck et al., 1996).

Procedure

Prospective Study: PWPs working within the IAPT services recruited and sought consent from service users on their case-load that were engaged in 'Step 2' interventions for depression. Each participant was asked to complete a BDI-II at their first and last treatment session and an ACS at every contact with the PWP, in addition to the self-report measures collected as standard at every contact within IAPT services (see above). PWPs then engaged the service users in treatment exactly as they would have done were they not participating in the present study with participation not impacting upon their treatment within the IAPT services in any way.

Analysis - The IAPT Services Database

Primary Outcomes: Relapse was defined on the basis of scores on the PHQ-9. Relapsers were those that scored above the cut-off for caseness at the start of their

treatment, below the cut-off for caseness at the end of their treatment, and then above the cut-off for caseness again on their return to the IAPT services. In addition, only those that experienced a clinically significant increase (50% or greater) in PHQ-9 score from end of treatment to the point of their return to the services were classified as having relapsed to depression.

A second primary outcome was also used: the presence or absence of 'residual symptoms' of depression post-treatment. Kroenke and colleagues (2001) report that a significant number of non-depressed individuals endorse several items on the PHQ-9, and as a result they suggest that scores between zero and four on the PHQ-9 all represent the absence of depressive symptomology. Therefore the presence of residual symptoms of depression was defined as obtaining a score of greater than four on the PHQ-9 at the end of treatment.

In addition to investigating the trajectory through the IAPT services of those that go on to relapse and those that have residual depressive symptoms at the end of treatment, two other sub-groups of those that returned to the service were used to inform the analyses relating to a latent profile analysis (see p.86). These were those that remained well after treatment, and those that failed to recover from their depressive episode both during their IAPT treatment and beyond. These two groups and those that relapsed to depression were identified from all service users that returned to the IAPT services over the study period. Returners were any service users that were discharged from the services for any reason and then had further sessions in the services any time from two weeks after their initial discharge.

In order to ensure the accuracy of the relapse and return variables the number of sessions post-discharge, the purpose and means of contact, the duration of the sessions and whether or not any self-report symptom measures were completed at these time points were recorded. Those with only one session post-discharge that lasted less than 15

minutes, or those with only a telephone contact with no symptoms measures completed (regardless of the duration) were not considered as having returned to the services, and therefore were not considered as potential relapsers.

Risk and Protective Factors: Due to the small number of relapsers many of the categorical variables such as ethnicity and marital status were recoded into binary variables.

Statistical Methods

All analyses were performed using STATA version 12.0. (StataCorp, 2011). Univariable logistic regression models were built independently to assess the effects of potential risk factors on relapse and residual symptoms respectively. Odds ratios (ORs) and 95% confidence intervals (CIs) are presented, and for continuous variables that were approximately normally distributed independent t-tests are also presented. Continuous variables were entered into the regression models as linear continuous variables with ORs representing the OR for a one-point increase in that variable (e.g. a one point increase in score on the PHQ-9). Multivariable logistic regression models were built with indicator variables entered on the basis of *a priori* assumptions (such as that the presence of residual symptoms would be predictive of relapse) and on the strength of univariable associations. Models were compared using Likelihood Ratio Tests (LRTs).

Survival analyses were conducted using the Kaplan-Meier method with Log-rank Tests (LR tests) used to consider the impact of risk-factors on the survival function of relapsers. Cox proportional hazards models were built using relapse as the dependent variable and time to relapse taken as the time from initial discharge from the services until the time at which criteria for relapse were met (either on or after return to services), measured in days. These Cox regression models were used to assess the impact of the risk factors identified from the logistic regression models on the hazard rate of relapse. Hazard ratios (HRs) and 95% CIs are presented.

An algorithm was developed (by Saunders, Cape, Fearon & Pilling, submitted) from an exploratory Latent Profile Analysis (LPA) of 16,636 service users who had treatment in the IAPT services between September 2008 and March 2012. The algorithm uses the posterior probabilities from the exploratory LPA to calculate the probabilities of membership to each of the eight profiles, and based on these probabilities determines which profile each individual run through the algorithm is most likely to belong to. It does this using information gathered at the start of treatment on the following variables: age, gender, ethnicity (treated as binary – 'White' or 'Non-White'), PHQ-9, GAD-7 and W&SAS scores (all treated as continuous variables), caseness on the IAPT Phobias scale (treated as a binary variable), whether or not the service user was prescribed psychotropic medications, and whether or not they were receiving benefits. For the present study the algorithm was used to determine the distributions of latent profile membership of relapsers, non-relapsers, those with residual symptoms, those that remained well after treatment, and those that failed to recover from their depressive episodes. The distribution of relapsers across the latent profiles was then compared with each of the other groups listed above using Chi-squared Goodness of Fit tests. Saunders and colleagues (submitted) also conducted a validation of the algorithm using a sample of 9,856 patients that had complete data at the end of treatment. This allowed those authors to determine the probability of recovery for each of the eight profiles, with those in profile 1 having the highest rate of recovery and those in profile 7 the lowest (Saunders et al., submitted). By comparing the proportions of each of the service users in the groups listed above across each of the eight profiles, it is possible to draw tentative conclusions about how well these profile memberships differentiate those in each of the identified groups. The results of this analysis might therefore inform us as to whether we can identify service users most at risk of relapse based only on information gathered at the start of their treatment and help the service consider means of structuring treatment in an attempt to reduce this risk.

Analysis – The Prospective Study

Primary Outcomes: For the prospective study the primary outcome was the presence or absence of residual symptoms of depression at the end of treatment. This was defined as described above.

Explanatory Factors: PHQ-9 and ACS scores at the start and end of treatment were used to derive change scores for each measure respectively. The pre-treatment scores and the change scores were then treated as explanatory factors to consider the relationship with residual symptoms of depression post-treatment.

Statistical Methods

All analyses were performed using STATA version 12.0. (StataCorp, 2011). Pearsons correlations were calculated for scores on the ACS and both BDI-II and PHQ-9 to consider whether any association between cognitive control and depressive symptomology was present. Linear and logistic regression models were used to determine whether ACS scores pre-treatment and the change in ACS score from start to end of treatment were predictive of the presence of residual symptoms post-treatment, controlling for the confounding effect of pre-treatment depressive symptomology. For linear regressions the proportion of the variance explained by the model (R^2), F-tests, and beta-coefficients with respective t-tests and p-values are presented. Logistic regressions used ACS scores and change scores entered as continuous variables and are presented as described above.

Ethical Approval

Ethical approval for both parts of the study was granted by the West London NHS Research Ethics Committee, reference number: 13/LO/0684, with local R&D approval granted by Noclor, Camden and Islington NHS Foundation Trust, reference number: 121619. Copies of letters confirming the ethical approvals can be found in Appendix VI.

Results

The IAPT Services Dataset

Descriptive Statistics

21,275 service users were referred to the IAPT services between December 2007 and May 2013 and met criteria for caseness on the PHQ-9 at the start of their treatment, Mean (SD) = 17.01(4.64). 92% of the sample also met criteria for caseness on the GAD-7 at the start of their treatment, Mean (SD) scores = 14.49(4.49). The sample had a Mean (SD) age at referral of 38.27(13.14) years. More than two-thirds of the sample were female 13,623 (66.24%), and of 'any white' ethnicity 12,876 (69.60%). Given the inclusion criteria the vast majority of the sample were referred with unipolar depressive disorders 14,726 (87.04%), of which 5,336 (31.54% of the whole sample) were referred with mixed anxiety and depression. More than two-thirds of the sample were engaged in 'Step 2' interventions (69.97%). One third of the sample received cognitive behavioural therapy (CBT) (33.20%) as their main treatment within the service, with 31% receiving guided self-help, and 15% involved in non-guided self-help interventions.

At the end of treatment 11,515 (54.25%) service users had residual symptoms of depression. A small number of the sample returned to the IAPT services for further treatment any time between their initial discharge and the end of May 2013 (522; 2.45%). 182 (34.87%) of these did not have a PHQ-9 score recorded at any point after their return to the services so could not be considered in the analysis of relapse to depression. It is unclear as to why there was no recorded PHQ-9 after returning to the services for these service users. There were no differences in symptom measure scores or number of sessions attended between those with and without a PHQ-9 score upon return. Those without a PHQ-9 score on their return were more likely to be treated at 'Step 3' (p=.0028). They also

cancelled more sessions (p=.0014) and 'did not attend' more sessions (p=.0009) than those with a PHQ-9 score upon their return.

Of the 355 returners that did have a PHQ-9 score recorded after their return 54 (15.21%) relapsed to depression, 155 (43.66%) remained recovered from their depressive episodes whilst 89 (25.07%) failed to recover from their depressive episode. It is unclear why those that remained recovered returned to the services. There were no differences with relapsers in terms of anxiety symptoms measure scores or levels of caseness on the GAD-7 (p=.069) or Phobias scale (p=.26), or in terms of the number of sessions attended post-return (p=.64). Compared to relapsers they were as likely to be attending for just one post-treatment review session, and as likely to be returning for anxiety related problems.

Residual Symptoms

Descriptive statistics and univariable associations between explanatory factors measured at the start of treatment and the presence or absence of residual symptoms of depression at the end of treatment can be found in Table 1. Similarly, descriptive statistics and univariable associations between explanatory factors measured at the end of treatment and residual symptoms of depression can be found in Table 2.

Table 1.
Comparison of those with and without residual symptoms of depression at the end of their treatment based on factors measured at the start of treatment.

Explanatory Factors		Non-residual symptoms N(%)	Residual Symptoms N(%)	OR(95%CI)	p-value
Total		**9,709(45.75)**	**11,515(54.25)**		
Demographics					
	Age at referral (years)	**Mean(SD)**	**Mean(SD)**	**t-test per 10-year increase**	
		37.97(13.32)	38.49(12.98)	*t*(21218)=2.91 1.03(1.01-1.05)	.005
	Sex				
	Male	3,181(34.01)	3,741(33.52)	1	.56
	Female	6,172(65.99)	7,421(66.48)	1.02(0.96-1.08)	
	Married/Civil Partnership				
	Yes	480(23.80)	674(25.41)	1	.21
	No	1,537(76.20)	1,979(74.59)	1.09(0.95-1.25)	
	Ethnicity				
	Any White Ethnicity	5,607(68.87)	7,231(70.14)	1	.064
	Non-White	2,543(31.13)	3,079(29.86)	0.94(0.88-1.00)	
	Employment Status				
	Employed	4,330(50.60)	5,629(49.60)	1	.16
	Not Employed	4,228(49.40)	5,720(50.40)	1.04(0.98-1.10)	
	Receiving Benefits				
	Yes	1,417(32.55)	2,075(33.43)	1	.046
	No	2,936(67.45)	3,952(65.57)	0.92(0.85-0.99)	
	Overall Diagnostic Group				
	Unipolar Depressive Disorders	6,441(86.62)	8,253(87.40)	1	.13
	Other	995(13.38)	1,190(12.60)	0.93(0.85-1.02)	
	Step at Start of Treatment				
	2	6,785(70.33)	7,967(69.79)	1	0.40
	3	2,863(29.67)	3,449(30.21)	1.03(0.97-1.09)	
	Depressive Symptoms	**Mean(SD)**	**Mean(SD)**	**t-test OR(95%CI)**	
	PHQ-9 Score	17.00(4.67)	17.57(4.60)	*t*(21222)=8.93 1.03(1.02-1.03)	<.0001
	General Anxiety Symptoms	**Mean(SD)**	**Mean(SD)**	**t-test OR(95%CI)**	
	GAD-7 Score	14.20(4.62)	14.72(4.37)	*t*(21111)=8.40 1.02(1.20-1.03)	<.0001
	GAD-7 Caseness				
	Yes	8,684(90.45)	10,719(93.11)	1.43(1.29-1.58)	<.0001
	No	917(9.55)	793(6.89)	1	
	Phobic Anxiety Symptoms	**Mean(SD)**	**Mean(SD)**	**t-test OR(95%CI)**	
	Social Anxiety Score	3.12(2.57)	3.42(2.57)	*t*(17916)=7.63 1.05(1.03-1.06)	<.0001
	Panic Score	2.55(2.72)	2.85(2.76)	*t*(17878)=7.31 1.04(1.03-1.05)	<.0001
	Specific Phobia Score	2.29(2.75)	2.49(2.78)	*t*(17871)=4.67 1.03(1.02-1.04)	<.0001
	Work and Social Adjustment	**Mean(SD)**	**Mean(SD)**	**t-test OR(95%CI)**	

W&SAS Score	20.46(9.18)	21.97(8.88)	*t*(17804)=10.86 1.02(1.02-1.02)	<.0001
Prescribed Medication				
Yes	3,965(45.53)	4,824(47.09)	1	.032
No	4,744(54.47)	5,420(52.91)	0.94(0.89-0.99)	
Long Term Health Condition				
Yes	552(7.61)	763(8.60)	1.14(1.02-1.28)	.023
No	6,699(92.39)	8,110(91.40)	1	

Note: Numbers do not add up to totals due to missing data

Table 2.

Comparison of those with residual of depression and those without residual symptoms based on factors measured at the end of treatment.

Explanatory Factors		Non-residual symptoms N(%)	Residual Symptoms N(%)	OR(95%CI)	p-value
Total		9,709(45.75)	11,515(54.25)		
Demographics					
	Employment Status				
	Employed	1,734(62.17)	5,341(49.67)	1	
	Not Employed	1,055(37.83)	5,384(50.33)	1.67(1.53-1.81)	<.0001
	Receiving Benefits				
	Yes	326(20.46)	1,945(35.68)	2.16(1.89-2.46)	
	No	1,267(79.54)	3,506(6432)	1	<.0001
Treatment					
	Step				
	2	3,231(61.29)	5,118(49.39)	1	<.0001
	3	2,041(38.71)	5,245(50.61)	1.62(1.52-1.74)	
	Stepped Up				
	Yes	719(13.68)	2,138(20.74)	1.65(1.51-1.81)	
	No	4,537(86.32)	8,170(79.26)	1	<.0001
	General Anxiety Symptoms	**Mean(SD)**	**Mean(SD)**	**t-test OR(95%CI)**	
	GAD-7 Score	3.13(2.75)	11.67(5.40)	*t*(13746)=74.14 1.72(1.68-1.76)	<.0001
	GAD-7 Caseness				
	Yes	131(5.66)	8,280(72.42)	43.78(35.46-54.06)	<.0001
	No	2,184(94.34)	3,153(27.58)	1	
	Clinically Significant Change in GAD-7				
	Yes	2,053(88.68)	2,609(22.82)	0.038(0.032-0.044)	<.0001
	No	262(11.32)	8,824(77.18)	1	
	Phobic Anxiety Symptoms	**Mean(SD)**	**Mean(SD)**	**t-test OR(95%CI)**	
	Social Anxiety Score	1.03(1.45)	3.11(2.44)	*t*(11572)=38.19 1.78(1.72-1.84)	<.0001
	Panic Score	0.70(1.36)	2.52(2.60)	*t*(11559)=31.48 1.61(1.55-1.66)	<.0001
	Specific Phobia Score	0.86(1.75)	2.19(2.60)	*t*(11538)=22.60 1.35(1.31-1.39)	<.0001
	Clinically Significant Change in Phobia Scale				
	Yes	1,315(60.88)	2,518(26.70)	0.23(0.21-2.60)	
	No	845(39.12)	6,911(73.30)	1	<.0001
	Work and Social Adjustment	**Mean(SD)**	**Mean(SD)**	**t-test OR(95%CI)**	
	W&SAS Score	5.94(5.74)	18.92(9.57)	*t*(11511)=60.62 1.26(1.25-1.27)	<.0001
	Clinically Significant Change in W&SAS				
	Yes	84(3.89)	197(2.11)	0.53(0.41-0.69)	
	No	2,078(96.11)	9,154(97.89)	1	<.0001
	Prescribed Medication				
	Yes	1,004(36.78)	3,994(47.01)	1	
	No	1,726(63.22)	4,502(52.99)	0.66(0.60-0.72)	<.0001
	Number of attended sessions	**Mean(SD)**	**Mean(SD)**	**t-test OR(95%CI)**	
		2.90(4.18)	6.47(5.67)	*t*(21222)=51.38 1.21(1.20-1.22)	<.0001
	Attended 10+ sessions				
	Yes	773(7.96)	2,527(21.95)	3.25(2.98-3.55)	<.0001

	No	8,936(92.04)	8,988(78.05)	1	
	Completed Treatment				
	Yes	3,024(31.15)	5,470(47.50)	2.00(1.89-2.12)	<.0001
	No	6,685(68.85)	6,045(52.50)	1	

Note: Numbers do not add up to totals due to missing data

Table 3.
Multivariable model of residual symptoms of depression post-treatment.

Risk Factor	OR(95%CI)*	p-value#
GAD-7 Caseness at End of Treatment		
Yes	6.76(5.12-8.92)	<.0001
No	1	
Clinically Significant Change in GAD-7 Score		
Yes	1	<.0001
No	5.53(4.47-6.84)	
W&SAS Caseness at End of Treatment		
Yes	4.52(3.34-6.12)	<.0001
No	1	
PHQ-9 Score at First Contact	1.09(1.07-1.11)	<.0001
Completed Treatment		
Yes	0.49(0.41-0.59)	<.0001
No	1	
Clinically Significant Change in Phobias Scale Score		
Yes	1	<.0001
No	1.63(1.41-1.90)	
Prescribed Medication at End of Treatment		
Yes	1.34(1.16-1.55)	.0001
No	1	
Phobia Scales Caseness at End of Treatment		
Yes	1.40(1.14-1.72)	.0012
No	1	
Attended 10 or More Sessions		
Yes	0.81(0.69-0.94)	.0054
No	1	

*Adjusted for GAD-7, W&SAS, and Phobias scale caseness at the end of treatment, clinically significant change in GAD-7 and Phobias scale scores, PHQ-9 score at the start of treatment, attending ten or more sessions, and being prescribed medication at the stage of ending treatment.
p-values from LRTs

The multivariable analyses combining pre-treatment and end of treatment factors revealed a logistic regression model predictive of the presence of residual symptoms at the end of treatment: Cox & Snell R^2=.42, Model $\chi^2(9)$=3515.36, p<.0001, N=8,403. Odds-ratios and LRT p-values for individual risk and protective factors are given in Table 3. Only factors with significant LRT p-values when testing a model with the factor included against a model without the factor included, were kept in the overall model.

Caseness on either the GAD-7 or Phobias scale at the end of treatment independently increased the odds of having residual symptoms of depression post-treatment. In addition to anxiety measure scores post-treatment, the PHQ-9 score recorded at the start of treatment and being on psychotropic medications at the end of treatment were also independent risk factors for residual symptoms. Completing treatment rather

than being discharged for any other reason and attending ten or more treatment sessions were protective factors: they conferred lower risk of having residual symptoms at the end of treatment. This model was used to inform the analysis of relapsers.

Relapse to Depression

Of those service users that had the potential to be classified as relapsing to depression (by being above the cut-off for caseness on the PHQ-9 at the start of treatment and below the cut-off for caseness on the PHQ-9 at the end of treatment), 54 met the criteria for having relapsed. These 54 were compared to 13,072 (99.59%) service users that either did not return or did not meet the inclusion criteria for relapse. Descriptive statistics and univariable associations between explanatory factors measured at the start of treatment and relapse are shown in Table 4, with descriptive statistics and univariable associations between explanatory factors measured at the end of treatment and relapse shown in Table 5. After their return relapsers had between one and 24 additional treatment sessions, Median (IQR) = 4(16).

Table 4.
Comparison of relapsers and non-relapsers based on factors measured at the start of treatment.

Explanatory Factors		Non-Relapsers N(%)	Relapsers N(%)	OR(95%CI)	p-value
Total		**13,072(99.59)**	**54(0.41)**		
Demographics					
	Age at referral (years)	**Mean(SD)**	**Mean(SD)**	**Per 10-year increase** 1.16(0.97-1.37)	
		37.89(13.63)	40.78(13.76)	**t-test** *t*(13124)=-1.58	.17
	Sex				
	Male	4,239(33.59)	22(41.51)	1	.22
	Female	8,380(66.41)	31(58.49)	0.71(0.41-1.23)	
	Married/Civil Partnership				
	Yes	699(25.13)	6(50.0)	2.98(0.96-9.27)	.048
	No	2082(74.87)	6(50.0)	1	
	Ethnicity				
	Any White Ethnicity	7,876(70.57)	40(78.43)	1	.22
	Non-White	3,285(29.43)	11(21.57)	0.66(0.34-1.29)	
	Employment Status				
	Employed	6,395(53.80)	27(50.0)	1	.58
	Not Employed	5,491(46.20)	27(50.0)	1.16	
	Receiving Benefits				
	Yes	1,836(29.41)	14(34.15)	1.24(0.65-2.38)	.51
	No	4,407(70.59)	27(65.85)	1	
Treatment					
	Overall Diagnostic Group				
	Unipolar Depressive	8,874(86.73)	37(78.72)	1	.11
	Other	1,358(13.27)	10(21.28)	1.77(0.88-3.56)	
	Step at First Treatment				
	2	9,133(70.27)	29(47.54)	1	.0001
	3	3,864(29.73)	32(52.46)	2.61(1.58-4.32)	
	Depressive Symptoms	**Mean(SD)**	**Mean(SD)**	**t-test OR(95%CI)**	
	PHQ-9 Score	16.60(4.59)	16.41(4.16)	*t*(13124)=0.30 0.99(0.93-1.05)	.76
	General Anxiety Symptoms	**Mean(SD)**	**Mean(SD)**	**t-test OR(95%CI)**	
	GAD-7 Score	13.97(4.59)	14.15(4.31)	*t*(13016)=-.28 1.01(0.95-1.07)	.78
	GAD-7 Caseness				
	Yes	11,682(90.11)	50(92.59)	1.37(0.49-3.80)	.54
	No	1,282(9.89)	4(7.41)	1	
	Phobic Anxiety Symptoms	**Mean(SD)**	**Mean(SD)**	**t-test OR(95%CI)**	
	Social Anxiety Score	2.99(2.50)	2.89(2.54)	*t*(10204)=0.30 0.98(0.88-1.10)	.76
	Panic Score	2.40(2.65)	2.72(2.70)	*t*(10176)=-0.88 1.04(0.95-1.15)	.34
	Specific Phobia Score	2.16(2.68)	2.15(2.62)	*t*(10176)=0.04 1.00(0.90-1.10)	.97
	Work and Social Adjustment	**Mean(SD)**	**Mean(SD)**	**t-test OR(95%CI)**	
	W&SAS Score	19.99(8.88)	20.24(9.18)	*t*(10128)=-0.21 1.00(0.97-1.03)	.84
	Prescribed Medication				
	Yes	5,140(43.91)	22(46.81)	1	.69
	No	6,565(56.09)	25(53.19)	0.89(0.50-1.58)	

Note: Numbers do not add up to totals due to missing data.

Table 5.
Comparison of relapsers and non-relapsers based on factors measured at the end of treatment.

Explanatory Factors		Non-Relapsers N(%)	Relapsers N(%)	OR(95%CI)	p-value
Total		**13,072(99.59)**	**54(0.41)**		
Demographics					
	Employment Status				
	Employed	3,768(62.70)	28(51.85)	1	.10
	Not Employed	2,242(37.30)	26(48.15)	1.56(0.91-2.67)	
	Receiving Benefits				
	Yes	725(21.58)	15(39.47)	1	.008
	No	2,635(78.42)	23(60.53)	0.42(0.22-0.81)	
Treatment					
	Step				
	2	4,852(57.98)	10(16.67)	1	
	3	3,517(42.02)	50(83.33)	6.90(3.49-13.64)	<.0001
	Stepped Up				
	Yes	1,288(15.27)	19(31.67)	2.57(1.49-4.45)	.0005
	No	7,145(84.73)	41(68.33)	1	
	Depressive Symptoms	**Mean(SD)**	**Mean(SD)**	**t-test OR(95%CI)**	
	PHQ-9 Score	2.25(3.12)	5.93(2.75)	*t*(13124)=-8.65 1.37(1.26-1.59)	<.0001
	Clinically Significant Change in PHQ-9 Score				
	Yes	12,617(96.52)	47(87.04)	0.24(0.11-0.54)	.0002
	No	455(3.48)	7(12.96)	1	
	Residual Symptoms on PHQ				
	Yes	3,387(25.89)	44(72.13)	7.41(4.22-13.00)	<.0001
	No	9,694(74.11)	17(27.87)	1	
	Any symptoms on PHQ				
	Yes	5,385(41.19)	52(96.30)	37.11(9.00-153.00)	<.0001
	No	7,687(58.81)	2(3.70)	1	
	General Anxiety Symptoms	**Mean(SD)**	**Mean(SD)**	**t-test OR(95%CI)**	
	GAD-7 Score	5.31(3.69)	8.00(3.70)	*t*(5722)=-5.28 1.16(1.10-1.23)	<.0001
	GAD-7 Caseness				
	Yes	1,263(22.27)	31(58.49)	4.92(2.83-8.54)	<.0001
	No	4,408(77.73)	22(41.51)	1	
	Clinically Significant Change in GAD-7 Score				
	Yes	3,884(68.49)	30(43.40)	0.60(0.35-1.04)	.067
	No	1,787(31.51)	23(56.60)	1	
	Phobic Anxiety Symptoms	**Mean(SD)**	**Mean(SD)**	**t-test OR(95%CI)**	
	Social Anxiety Score	1.51(1.70)	2.40(1.89)	*t*(5190)=3.75 1.28(1.11-1.42)	.0002
	Panic Score	1.04(1.65)	1.85(2.02)	*t*(5183)=3.56 1.23(1.10-1.39)	.0004
	Specific Phobia Score	1.10(1.92)	1,42(2.08)	*t*(5184)=1.21 1.08(0.95-1.22)	.23
	Clinically Significant Change in Phobia Scales Score				
	Yes	2,551(49.62)	20(37.74)	0.62(0.35-1.08)	.085
	No	2,590(50.38)	33(62.26)	1	
	Work and Social Adjustment	**Mean(SD)**	**Mean(SD)**	**t-test OR(95%CI)**	
	W&SAS Score	9.59(7.16)	13.15(8.16)	*t*(5184)=3.57 1.06(1.03-1.10)	.0004
	Clinically Significant Change in W&SAS Score				
	Yes	194(3.78)	0		.15
	No	4,940(96.22)	52(100)		
	Prescribed Medication				
	Yes	1,945(37.13)	13(35.14)	0.92(0.47-1.81)	.80

No	3,294(62.87)	24(64.86)	1	
Number of attended sessions	**Mean(SD)**	**Mean(SD)**	**t-test OR(95%CI)**	
	4.05(5.02)	16.13(7.19)	*t*(13124)=17.62 1.18(1.15-1.21)	<.0001
Attended 10+ sessions				
Yes	1,672(12.79)	42(77.78)	23.86(12.48-45.65)	<.0001
No	11,400(87.21)	12(22.22)	1	
Completed Treatment				
Yes	5,207(39.83)	44(81.48)	6.65(3.34-13.23)	<.0001
No	7,865(60.17)	10(18.52)	1	

Note: Numbers do not add up to totals due to missing data.

Multivariable analyses revealed two separate logistic regression models predictive of relapse, shown in Table 6 and Table 7 respectively. Both models are presented and describe potentially different relationships with relapse to depression. Table 6 shows that the presence of residual symptoms of depression and having attended ten or more sessions during contact with the IAPT services was predictive of relapse: Cox & Snell R^2=.20, Model $\chi^2(2)$=152.32, p<.0001, N=13,142. No other factors were retained in the model. Table 7 shows an alternative model. For the smaller number of service users with a recorded GAD-7 score at the end of treatment, this score was a more important risk factor for relapse than was the presence of residual symptoms on the PHQ-9 at the end of treatment. In addition, being in receipt of social-welfare 'benefits' and having completed treatment compared to having been discharged for any other reason were independent risk factors for relapse. Cox & Snell R^2=.20, Model $\chi^2(2)$=88.23, p<.0001, N=3,299. As so many service users were missing a GAD-7 at the end of treatment, further analyses were performed to consider why this may be the case and whether or not those with and without a GAD-7 score are distinct enough to suggest they represent different populations of those that go on to relapse.

There were 7,402 service users missing a GAD-7 score at the time of their discharge from the IAPT services. Compared to those with a recorded GAD-7 score those missing a GAD-7 at the end of treatment attended fewer sessions (Mean (SD) =1.26 (1.10) compared to 6.80 (5.75), p<.0001)) and were more likely to be engaged in non-guided self-help

interventions (40% compared to 4%). They therefore had fewer face-to-face contacts in which to complete the GAD-7. Those missing the GAD-7 at the end of treatment were also less likely to have a diagnosis of anxiety disorders (2.51% compared to 6.01%) or mixed anxiety and depression (21.47% compared to 29.81%), and they had significantly higher PHQ-9 scores at the beginning of treatment compared to those with a GAD-7 score (Mean (SD) = 17.58 (4.66) and 15.32 (4.17) respectively, p<.0001). Although for these analyses only those at or above caseness on the PHQ-9 at the start of treatment and below caseness at the time of discharge were included, service users missing a GAD-7 score at the end of treatment were more likely to have had a clinically significant change in PHQ-9 score from start to end of treatment compared to those with a recorded GAD-7 score at the end of treatment (100% compared to 92%, p<.001). It appears probable therefore that those missing a GAD-7 at the end of their treatment were more likely to be treated specifically for depression alone (rather than for a mixture of anxiety and depression or for a construct overlapping the two conditions such as low self-esteem or wellbeing) and this may have influenced the decision either of their treating clinicians or of the service user themselves to not complete a post-treatment GAD-7.

Table 6.
Multivariable model of explanatory factors measured at the end of treatment as risk factors for having relapsed to depression, based on all 13,142 service users that had the potential to relapse.

Risk Factor	OR(95%CI)*	p-value‡
Attended ten or more sessions		
Yes	16.90(8.87-32.19)	<.0001
No	1	
Residual Symptoms on PHQ at end of treatment		
Yes	3.13(1.73-5.65)	.0001
No	1	

*Adjusted for attending ten or more treatment sessions and residual symptoms of depression
‡ p-values from LRTs

Table 7.
Alternative multivariable model of relapse based on 3,299 service users with a recorded GAD-7 score at the end of treatment.

Risk Factor	OR(95%CI)*	p-value‡
GAD-7 Caseness at End of Treatment		
Yes	7.01(3.53-13.91)	<.0001
No	1	
Number of Attended Sessions	1.14(1.10-1.18)	<.0001
Receiving Benefits at End of Treatment		
Yes	2.51(1.26-5.00)	0.009
No	1	
Completed Treatment		
Yes	4.79(1.09-21.13)	0.038
No	1	

*Adjusted GAD-7 caseness at the end of treatment, the number of session attended receiving benefits and completing treatment.
‡ p-values from LRTs

As well as considering risk factors for relapsing at any point post-treatment, analyses were conducted to determine risk factors for relapsing more quickly; what factors effect survival without relapse; and what affects the hazard rate of relapse. Survival analyses were performed with univariable tests of the factors identified in the above multivariable logistic regression models used as a starting point for considering which factors might effect survival time.

Survival Analysis of Relapsers

Kaplan-Meier survival analysis methods were used to compare relapsers to all those that were depressed at the start of treatment and not at the end of treatment. The number of days from the time of the initial discharge to relapse ranged from 14 to 674 days with a Mean (SD) of 128.67 (123.73) and median of 98 days. Cumulative percentages of time to relapse were as follows: 5% relapsed within 18 days, 10% within 28 days, 25% within 59 days, 50% within 98 days, 75% within 151 days, 90% within 239 days, 95% within 336 days, and 99% within 674 days.

Independent t-tests were used to compare mean survival in days by the factors identified in the logistic regression models described above. Those with residual symptoms of depression at the end of treatment (Mean (SD) = 99.33 (72.18) days) relapsed more

quickly than those without residual symptoms of depression (Mean (SD) = 209.44 (221.04) days), *t*(54)=2.83, *p*=.0066. Those that met criteria for caseness on the GAD-7 at the end of treatment (Mean (SD) = 91.42 (98.58) days) relapsed more quickly than those that did not (Mean (SD) = 182.13 (170.88) days) *t*(53)=2.47, *p*=.017. There were non-significant differences in the survival time of those that attended ten or more sessions (Mean (SD) = 148.12(154.30) compared to those that did not (Mean (SD) = 73.46(39.84) (t(54)=1.72, p=.092), those that completed treatment (Mean (SD) = 140.06(149.73) days) compared to those that did not (Mean (SD) = 82.33(47.67) days) (*t*(54)=1.14, p=.26), and those receiving benefits (Mean (SD) = 100.9(75.83)) compared to those not receiving benefits at the time of initial discharge (Mean (SD) = 153.09(175.01)), (*t*(37)=1.12, p=.27).

Log rank tests showed significant differences in survival functions for those with and without residual symptoms at the end of treatment (p=.027) (see Figure 1), those meeting criteria for caseness on the GAD-7 at end of treatment and those not (p=.0061) (See Figure 2), and for those attending less than ten sessions compared to those attending more than ten (p=.0082) (See Figure 3). There was no difference in survival function for those receiving or not receiving benefits at the time of their discharge from IAPT services (p=.38), or for those that did or did not leave due to completing treatment (p=.075).

Figure 1.
Kaplan-Meier survival estimates of relapsers split by residual symptoms of depression at the end of treatment.

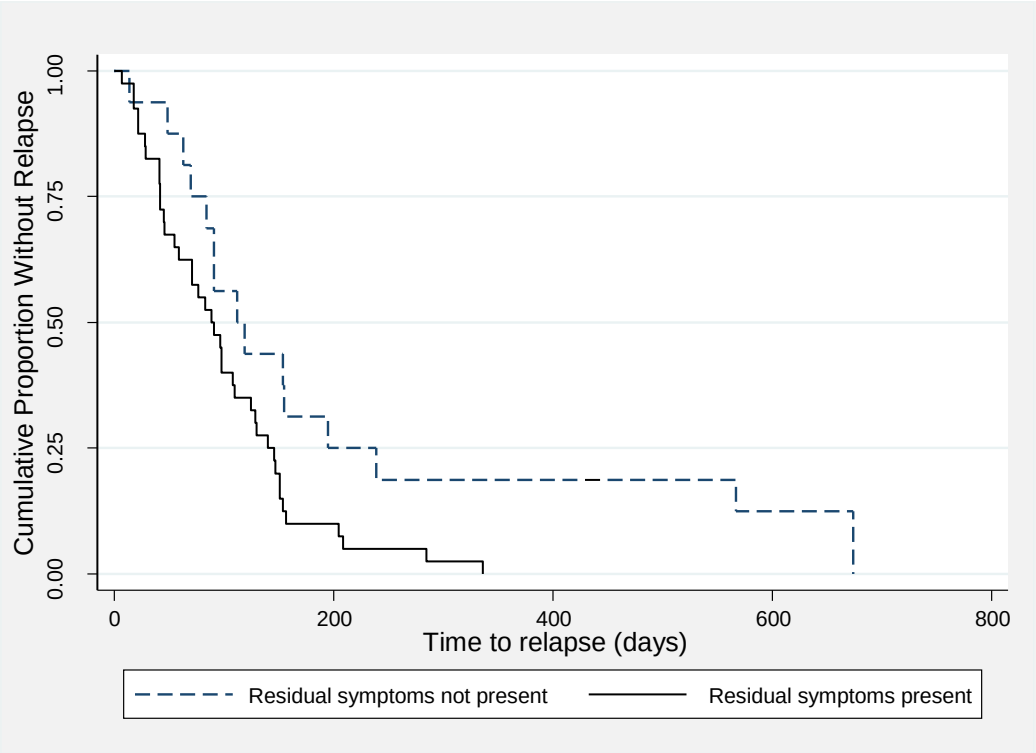


Figure 2.
Kaplan-Meier survival estimates of relapsers split by caseness on the GAD-7 at the end of treatment.

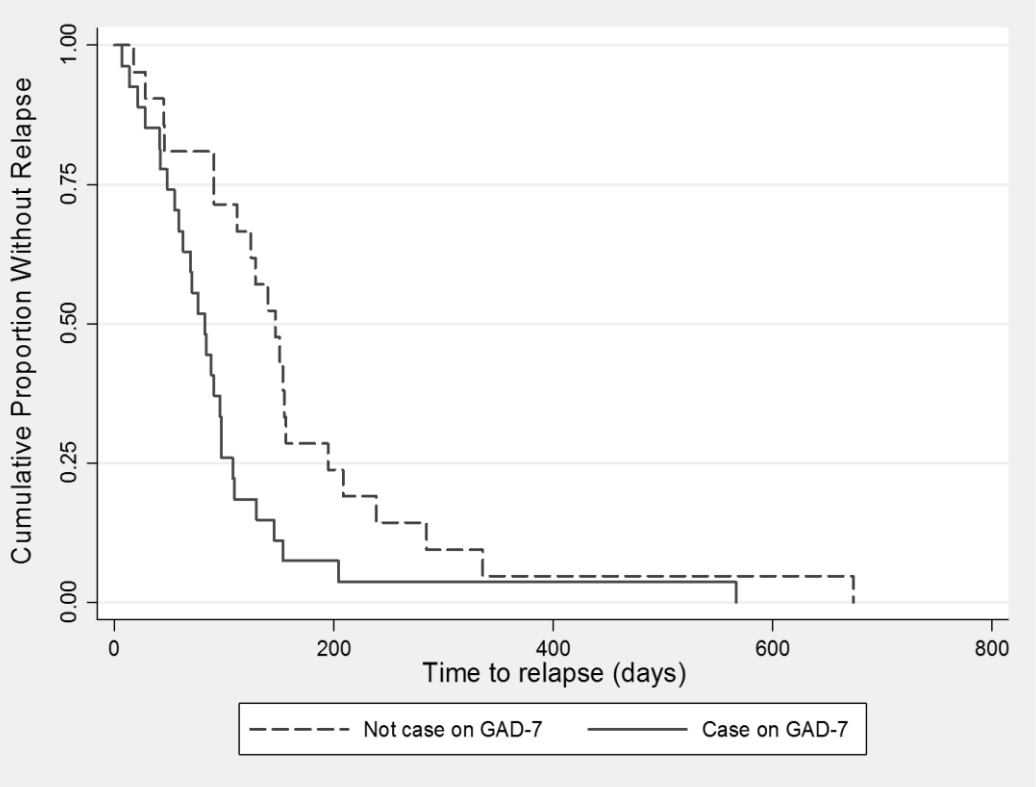
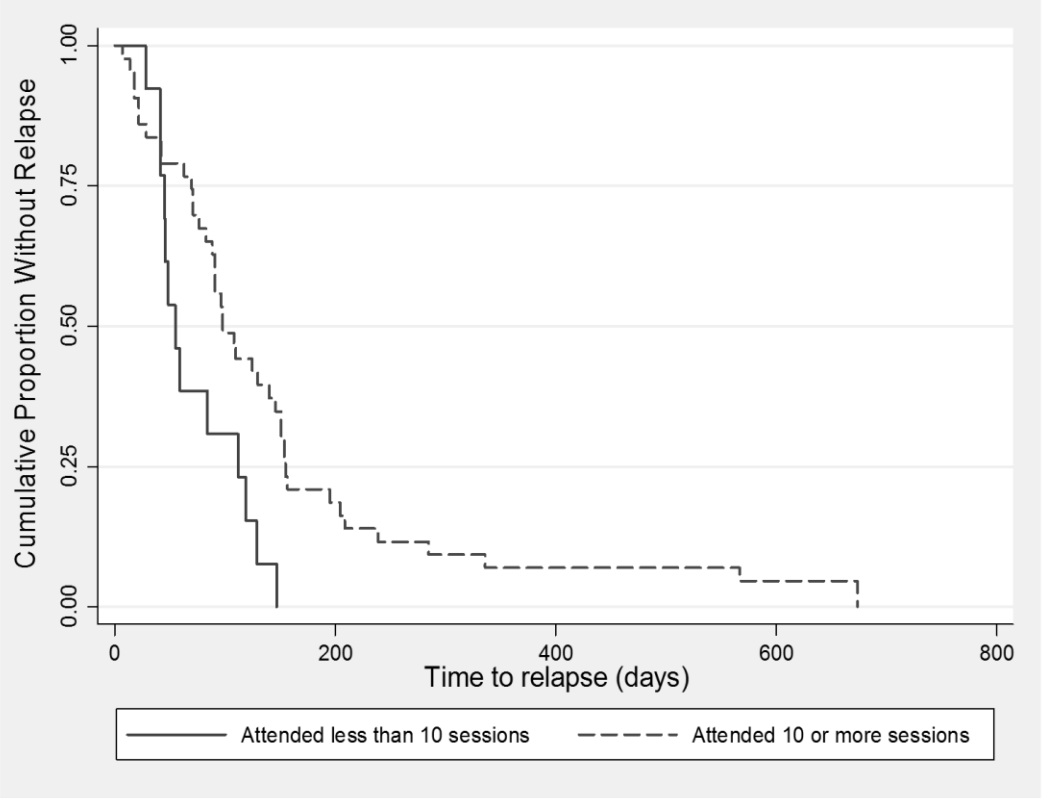


Figure 3.
Kaplan-Meier survival estimates of relapsers split by attending ten or more sessions of treatment.



A Cox proportional hazards model was built to consider the multivariable impact of the risk factors identified above on the hazard rate of relapse, Wald χ^2 (4)=20.91, *p*=.0003. The model consisted of a total of 5,948 days at risk with 42 relapses over that period, and showed that caseness on the GAD-7 at the end of treatment, attending less than ten session of treatment, being in receipt of benefits at the end of treatment, and younger age were all related to a greater hazard rate of relapse.

Table 8.
Cox proportional hazards model of relapse to depression after treatment.

Risk Factor	HR(95%CI)*	p-value‡
GAD-7 Caseness at End of Treatment		
Yes	3.53(1.76-7.30)	<.0001
No	1	
Receiving Benefits at End of Treatment		
Yes	2.74(1.28-5.86)	.009
No	1	
Attended Ten or More Sessions		
Yes	1	.016
No	3.32(1.26-8.80)	
Age at referral (by one year increase)	0.97(0.94-0.99)	.038

*Adjusted for GAD-7 caseness at the end of treatment, receiving benefits at the end of treatment, attending ten or more treatment sessions, and age at referral.
‡ p-values from LRTs

To this point the analyses have concerned risk for relapse or a proxy of this (residual symptoms post-treatment) based on factors primarily measured at the end of treatment. Pre-treatment factors have been considered, though when entered in to multi-variable models they had little impact upon either the odds of relapse or the rate of relapse. However, additional analyses were conducted using an algorithm based on a LPA conducted by Saunders et al. (submitted). The algorithm uses variables measured pre-treatment only to determine membership to one of eight latent profiles, from which recommendations regarding the likely trajectory of service users from start to end of treatment can be made. Using this algorithm to determine the distribution of service users across the eight latent profiles in each of the groups relevant to the present study (outlined below), it is possible to draw tentative conclusions regarding the ability of this algorithm to be utilised to identify those at greatest risk of relapse pre-treatment.

Use of Algorithm Based on a Latent Profile Analysis

The algorithm developed by Saunders and colleagues (submitted) was used to determine the proportions of each of the following groups of service users across each of the eight latent profiles: relapsers; non-relapsers; those with residual symptoms at the end of treatment; those that returned to the services but were not depressed on their return (i.e. those that remained well); and those that returned to the service as depressed but were never considered in the analysis of relapsers as they were depressed at the end of their treatment (i.e. those that stayed depressed). Using the distribution of relapsers across the latent profiles as a basis for comparison, there were differences in the distributions of profiles between the relapsers and non-relapsers: $\chi^2(7)=93443.37$, $p<.0001$, and between relapsers and those that remained recovered: $\chi^2(6)=17.96$, $p=.006$, but not between relapsers and those that stayed depressed: $\chi^2(6)=7.20$, $p=.41$, or between relapsers and those that had residual symptoms: $\chi^2(6)=8.75$, $p=.27$. Further inspecting Table 9, it can be seen that none of those that the algorithm determined are most likely to be assigned to profile 1 belonged to the relapsers or stayed depressed groups. For profile 2 there was a greater probability of belonging to the remained recovered group. Those in profile 7 were far more likely to belong to the stayed depressed group than all other groups, with the biggest difference being between this group and those in the remained recovered group.

Table 9.
Distribution of patients throughout the eight latent profiles by their group status.

Latent Profile Assignment	Non-relapsers N(%)	Relapsers N(%)	Residual Symptoms Present N(%)	Remained Recovered N(%)	Stayed Depressed N(%)
	13,072	**54**	**11,515**	**155**	**89**
Profile 1	350(2.68)	0	153(1.33)	1(0.65)	0
Profile 2	3331(25.48)	13(24.07)	2279(19.79)	52(33.55)	8(8.99)
Profile 3	58(0.44)	1(1.85)	31(0.27)	0	0
Profile 4	608(4.65)	2(3.70)	378(3.28)	7(4.52)	2(2.24)
Profile 5	1457(11.15)	7(12.96)	1478(12.84)	25(16.13)	17(19.10)
Profile 6	1540(11.78)	7(12.96)	1218(10.58)	17(10.97)	7(7.89)
Profile 7	1897(14.51)	6(11.11)	2352(20.43)	8(5.16)	33(37.08)
Profile 8	3831(29.31)	18(33.33)	3626(31.49)	45(29.03)	22(24.72)

Prospective Study

In addition to the analyses of residual symptoms and relapsers from the IAPT dataset, a prospective study was conducted to collect data on a factor proposed as playing a key role in relapse - cognitive control - in order to investigate the relationship between cognitive control and being at greater risk of relapse post-treatment by having residual symptoms of depression.

Descriptive Statistics

Between September 2013 and April 2014 64 patients were recruited to the prospective study. The majority of respondents were female (39(70.91%)), ethnically 'white' (41(77.36%)), with ages at referral ranging from 17-65 years old (Mean (SD) =35.36(12.15)). Scores on the symptoms measures at the start of treatment were as follows: PHQ-9 Mean (SD) = 16.25(5.26), GAD-7 Mean (SD)=13.05(4.94) with 76.36% of respondents reaching caseness, BDI-II Mean (SD) = 29.68(10.97) (completed by only 38(59.38%) participants)) with the majority of respondents in either the moderately depressed (10(26.32%)) or severely depressed (22(57.89%)) categories. Scores on the ACS at the beginning of treatment ranged between 25 and 66, Mean (SD)=45.82(9.13).

Study participants attended between 1-18 sessions within the IAPT services (Mean (SD) = 5.41 (2.72)), with 42 (65.62%) completing treatment during the study period. Eight (17.02%) participants were stepped up from Step 2 to Step 3 during the course of the study.

Thirty-five of the 42 participants that completed treatment over the study period completed an end of treatment PHQ-9, with 20 (57.14%) still at or above caseness for depression and 15 (42.86%) below caseness, having recovered from their depressive episode based on PHQ-9 scores.

Comparison with Population from which the Sample was Drawn

A population of 3,292 service users were eligible for the prospective study. From this a sample of 64 (1.94%) service users were recruited. There were no differences between those recruited and those not recruited in terms of gender (p=.38), primary diagnosis (p=.20), proportions of those prescribed psychotropic medications at the start of their treatment (p=.42), or start of treatment symptoms measures: PHQ-9 scores (p=.36), GAD-7 scores (p=.53), level of caseness of on the phobias scales (p=.032), and W&SAS score (p=.16). However, those recruited were less likely to be of non-white ethnicity than those not recruited (12.50% and 35.51% respectively, p=.002) and were on average younger (Mean (SD) = 33.45 (12.03) years old) than those not recruited (Mean (SD) = 38.03 (13.37) years old), $t(3290)=2.56$, $p=.024$.

Relationship Between Cognitive Control and Depressive Symptoms

Across all participants, scores on the ACS and BDI-II were highly correlated $r=-0.67$, n=40, $p<.0001$. However, only 12 BDI-IIs were completed at the end of treatment so analyses use end of treatment PHQ-9 scores instead. Scores on the ACS and PHQ-9 were moderately correlated at the start of treatment $r=-0.55$, n=43, $p=.0001$ and at the end of treatment $r=-.48$, n=36, $p=.0033$.

For the ACS change scores were calculated by subtracting the start of treatment score from the end of treatment score, and for the PHQ-9 they were calculated by subtracting the end of treatment score from the start of treatment score. There was a moderate correlation between the change in PHQ-9 scores and change in ACS scores from beginning to end of treatment r=0.59, n=31, p=.0004. There was a difference in the direction and degree of change in the ACS scores for those that recovered from their depressive episode based on PHQ-9 scores from start to end of their treatment. The Mean (SD) change in ACS score for those that did not recover from their depressive episode was -3.26 (7.16) points (the minus number indicating their scores on the ACS decreased from the start of treatment to the end of treatment). This is compared to a Mean (SD) change of 4.25(7.36) points on the ACS for those that recovered from their depressive episodes, t(29)=2.81, p=.0087. In addition, taking just those that experienced a positive change of any degree in ACS score from start to end of treatment was associated with a greater probability of recovery from depression from start to end of treatment (OR (95%CI) = 5.60 (0.98-32.11), p=.029).

Of those that completed treatment 78% had residual symptoms of depression at the end of their treatment, predicted by the degree of change in participant's ACS scores from the start to the end of their treatment after controlling for baseline levels of depression, R^2=.29, F(2,28)=5.63, b=-.024, t(30)=-2.75, p=.010. For every one point increase in ACS score after controlling for PHQ-9 scores at the start of treatment, the odds of having residual symptoms decreased (OR (95%CI) = 0.79 (0.65-0.97), p=.025.

ACS scores at the start of treatment were used to prospectively predict the presence of residual symptoms at the end of treatment, though this effect was non-significant after controlling for PHQ-9 scores at the start of treatment: R^2=.25, F(2,40)=6.62, p=.0033, b=-0.009, t(42)=-2.72, p=.26.

Discussion

Key Findings

Residual symptoms were found to be an important predictor of relapse to depression and of relapsing more quickly. Attending ten or more sessions was also a predictor of relapse (though attending fewer than ten was associated with an increased hazard rate of relapse).

A minority of service users had a GAD-7 score recorded at the end of treatment; for those that did, the presence of residual symptoms on the PHQ-9 was no longer an important predictor of relapse. GAD-7 score at the end of treatment was the strongest predictor of relapse. Other important factors to increase the risk of relapse were having attended more treatment sessions, having completed treatment, and being in receipt of benefits at the time of ending treatment.

More than three-quarters of relapses occurred within six months of discharge from the IAPT services. As well as higher PHQ-9 scores at the beginning of treatment, higher GAD-7 scores, attending fewer than ten treatment sessions, not completing treatment, and being in receipt of benefits were all risk factors for relapsing more quickly and were related to a higher hazard rate of relapse.

The latent profiles of those that relapsed were different from non-relapsers and those that remained recovered, though not from those that had residual symptoms at the end of treatment or those that stayed depressed throughout treatment and beyond.

The prospective study found that the level of self-reported cognitive control changes as the level of self-reported symptoms of depression also change. There were differences in the direction and degree of change in cognitive control for those that recovered from their depressive episode over the course of treatment compared to those that did not. Both the magnitude of change in cognitive control and the absolute level of cognitive control post-treatment can be used to predict the presence of residual symptoms

of depression at the end of treatment after controlling for baseline depression, though the level of cognitive control at the start of treatment cannot.

Interpretation

The IAPT Dataset Analysis

Finding that residual symptoms are related to the risk of relapse is in keeping with the wider literature (Buckman et al., submitted; Campbell, 2009). However, the findings relating to the relationship between symptoms of anxiety at the end of treatment and relapse to depression were unexpected. Given the high number of service users missing a GAD-7 score at the end of treatment, it may be that those with a recorded score represent an important and substantially different sub-group of the population of IAPT patients presenting with depression at the start of treatment. The fact that those with a recorded GAD-7 score were more likely to present to services with anxiety disorders or mixed anxiety and depression, were seen for more sessions, and proportionally fewer of them experienced clinically significant changes in their PHQ-9 scores pre-treatment to post-treatment, suggests that they may well have been engaged in more anxiety focussed interventions despite their depression. If this is the case it may be that there was some systematic bias by clinicians in the services asking far fewer service users treated only for depression to complete GAD-7s compared to those they were treating for primary or secondary anxiety disorders. Nonetheless, for this sub-group residual symptoms of anxiety were more strongly predictive of relapse to depression than were residual depressive symptoms. Given the higher number of this sub-group originally diagnosed with mixed anxiety and depression, it might be the case that relapses (which were determined only by PHQ-9 scores, not by anxiety symptom measures) were of the same nature as their index episodes, though this was not measured in the present study.

Finding that attending more treatment sessions was related to a greater risk of relapse, but those that attended fewer than ten sessions relapsed more quickly than those that attended ten or more, may be explained by the fact that most of the relapsers were treated at Step 3. Step 3 interventions tend to include a greater number of sessions than are offered at Step 2, reflecting the fact that at Step 3 service users tend to be suffering either with more complex and difficult to treat disorders (such as posttraumatic stress disorder) or with higher levels of disorder and dysfunction than service users treated at Step 2. Levels of symptom severity and dysfunction did not differ between relapsers and non-relapsers at the start of treatment. However, proportionately twice as many relapsers were stepped up from Step 2 to Step 3 during the course of their treatment compared to non-relapsers and their mean end of treatment symptom measure scores were significantly higher than those of the non-relapsers (across all measures), which may explain the findings related to the numbers of sessions attended.

Finding that those completing their treatment were likely to survive without relapse longer than those not completing their treatment was expected and may further explain the findings related to number of sessions attended. Attending more treatment sessions and completing treatment might confer benefit in preventing relapse given that a greater number of therapeutic interventions can be delivered, including specific relapse prevention techniques that tend to be covered towards the end of treatment, and/or greater time spent focussing on particular interventions which might make the difference in preventing relapse. In addition, among those not completing treatment are service users that declined treatment after having started it and others that self-discharged. These factors might describe a population that were not finding treatment useful for them or that were not able to engage appropriately in it at that time. As a whole group they might therefore have been more likely to relapse more quickly, but they may also have been less likely to re-present to the same services for treatment when any relapses occurred, thus

may have been underrepresented in the relapser group as a whole so seemingly being at lower risk of relapse overall. The relationship between receiving social-welfare 'benefits' at the time of discharge and relapse is somewhat more difficult to interpret and requires further investigation for sound conclusions about this relationship to be drawn. It may be the case that this is a proxy variable for factors commonly associated with adverse health outcomes such as lower socio-economic status or lower educational attainment (Adler & Ostrove, 1999), though this is by no means assured.

As the latent profile of relapsers was significantly different from non-relapsers, it is plausible that the algorithm developed by Saunders et al (submitted) may be used to help identify service users at greater risk of relapse based on pre-treatment factors alone. However, as the profiles of relapsers were not different from those that stayed depressed throughout their contact with the services, it may be that the algorithm is of less use in differentiating those that have a higher likelihood of relapse from those that are likely to not do well/not recover from their episode by the end of IAPT treatment.

Prospective Study

The findings relating to cognitive control are in keeping with the wider literature based on laboratory and neuroimaging studies as cognitive control has been considered by several authors to play a pivotal role in the neural mechanisms of depression (e.g. Roiser et al., 2012).

Strengths and Limitations

There were two separate elements to this study.

The secondary analysis of the IAPT services dataset: Perhaps the greatest limitation of this secondary data-analysis is that significant selection biases may have been introduced in the analysis of relapsers. Epidemiological studies suggest approximately two-thirds of patients treated for depression will relapse within two-years of completing

treatment (e.g. Mueller et al., 1999). Given that this study included all service users seen within the IAPT services over a five year period, having a sample of just 54 relapsers from a potential 13,142 suggests that a great number of relapses have occurred without service users being re-referred to these IAPT services. However, given that the only difference between relapsers and non-relapsers prior to starting treatment was found to be their marital status, it is likely that the relapser group does sufficiently represent IAPT service users treated for depression.

Despite the small number of relapsers this study was able to confirm expectations from the wider literature relating to residual symptoms and relapse to depression, and was also able to identify risk factors for a potentially distinct sub-group of relapsers not previously described in the literature on relapse to depression in adults. However, due to the limitations of a secondary data analysis and given that the history of depression in each patient is not routinely measured in the IAPT services, as with previous studies the present study took no account of whether service users were presenting to the services with their first lifetime episode of depression or any subsequent episode. As such, the study was unable to differentiate between those that had previously experienced relapse(s) to depression and those that were experiencing their first depressive relapse. This may have led to the conflating of results from these potentially different groups, thus introducing significant bias (Monroe & Harkness, 2005). Similarly, the IAPT services do not routinely ask service users about a history of childhood maltreatment. The present study was therefore not able to include this factor in any analyses. As this has been shown to be an important predictor of relapse (Buckman et al., submitted), it may well be that some of the relationship between the factors identified as conferring risk for relapse in the present study might have been attributable to the unmeasured confounding effect of childhood maltreatment.

The present study included analyses of multiple explanatory and outcome variables, increasing the probability of Type 1 errors. As recommended by Rothman (1990), Bonferroni (or equivalent) adjustments were not made as these assume that data are independent. However, given the strength of the associations and p-values returned by most of the inferential tests it is unlikely that these associations were due to chance alone. This is despite the small number of relapsers and therefore low power in the analyses.

There were no significant interactions found between any of the variables identified in the multivariable models (interaction data are not presented in the results section), suggesting that the observed effects are not due to effect modification. However, along with the known factors which may be confounding the relationships observed, such as childhood maltreatment, there may be several unknown confounders of the relationship not accounted for in the present study.

The prospective study: This is the first study (known to this author) to have prospectively measured cognitive control and symptoms of depression in the context of a routine clinical setting. In so doing the study has shown that cognitive control can be measured quickly with a self-report measure, and with utility. In addition unlike many previous studies of relapse to depression, the present study focussed on primary care patients, many of whom had not only unipolar depression but also comorbid anxiety problems, and so findings should be generalizable to the wider population presenting with depression in UK health services.

As with the secondary data-analysis it is possible that significant selection biases may have been introduced in the prospective study analyses. Only 64 participants were recruited to the study from 3,292 service users that were eligible. Prospective study participants were not randomly selected, thus the possibility of further significant selection bias cannot be ruled out. However, no differences were found on any of the symptom measures between the prospective study sample and the population from which the

sample was drawn. There were differences in age and ethnicity, though the impact of these factors is difficult to determine. However, neither age nor ethnicity were found to be risk factors for having residual symptoms of depression post-treatment nor for relapse in the secondary data-analysis.

Conclusions and Implications

This is the first study in a clinical setting (known to this author) to use a self-report measure of cognitive control to show that levels of cognitive control change in accordance with levels of depressive symptoms. It is also the first study to prospectively measure cognitive control alongside depressive symptoms in the context of routine clinical practice, therefore being able to show that cognitive control can be used to predict levels of depressive symptoms post-treatment. However, relapse was not measured prospectively in accordance with cognitive control and so the exact nature of the relationship between these factors is yet to be determined. To this end the prospective study will continue to collect data for up to one year post-treatment for each of the recruited service users; on the basis of findings from the survival analysis it can be expected that approximately 95% of relapsers will be captured in this time period.

While for the majority of patients residual symptoms of depression are the most important predictor of relapse to depression, for those with significant comorbid levels of anxiety it may be that residual symptoms of anxiety represents a more important predictor of relapse. In addition, several treatment-related and socio-demographic factors have been found to be related to relapse for the first time such as being in receipt of benefits. The exact nature of these relationships is difficult to determine and may warrant further investigation in future studies. Furthermore, this is the first study to relate an algorithm based on a Latent Profile Analysis of IAPT service users with outcomes beyond the end of treatment. It showed that use of the algorithm can help differentiate between those most likely to benefit from treatment within the IAPT services and remain recovered and those

that are most likely to either not benefit from IAPT treatment by staying depressed, or those that will benefit at the point of discharge but that may be at greater risk of relapsing post-treatment. This suggests that a prospective study trialling the use of this algorithm is warranted.

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Part 3: Critical Appraisal

Overview

This critical appraisal will focus on three areas of import to the conducting of the prospective study reported on above and one area related to the analysis of the inner London Trust's Improving Access to Psychological Therapies (IAPT) services database. Firstly, the appraisal will focus on the theoretical underpinnings of the research and discuss why conducting research in this field, in this manner, is particularly important. Secondly, it will discuss the context in which the research was carried out and how this impacted upon the research process. Thirdly, the appraisal will discuss some of the methodological choices made in conducting the research, potential problems as a result of these choices and considerations on the implications of the research in relation to these choices.

Theoretical Considerations and Background

The research literature on relapse to depression has to date delivered little in the way of usable interventions in clinical settings to prevent relapse (Clarke et al., in press). There is surprisingly little research in this area given that the problem of relapse has been recognised for many decades; it is now nearly two decades since the start of the global burden of disease study which reported that depression is one of the largest contributors to life lost world-wide including adjustment for years of life lived with disability (Murray & Lopez, 1996). Much of the extant literature on relapse to depression has taken one of two forms: there are a number of epidemiological studies using large cohorts of depressed patients to determine risk factors for relapse, particularly focussing on socio-demographics and life events; and there are a number of theoretically informed clinical trials which have used prospective follow-up to create nested case-control studies after breaking randomisation. From this literature has come a perhaps somewhat self-perpetuating consensus view that relapse can only be predicted by the presence of residual symptoms of depression post-treatment and by a history of multiple previous episodes of depression (Campbell, 2009). Added to this there is the view that stressful life events play a part in

relapse, but there is no consensus as to whether a stress-generation or autonomy-stress model fits best and both have been equally supported in prospective studies (e.g. Monroe & Harkness, 2005). This consensus view though has offered little to clinicians seeking to help their clients prevent or stave off relapse.

It is almost tautological to state that residual symptoms of depression are the biggest risk factor for relapse. In addition, despite residual symptoms having been so reliably linked with relapse, the literature has to date not answered questions such as what degree of residual symptoms are important for predicting relapse; and whether there is a critical/tipping point before which risk for relapse is negligible and beyond which it increases greatly. There is also no consensus on what kind of symptoms are most important or if all are equally important, and there is no clear line on what sort of depression and what sort of relapses clients experience. There have been many proposed subdivisions of the diagnostic category of depression including diagnoses such as: 'anxious depression', 'atypical depression', 'endogenous depression', 'melancholic depression', 'reactive depression', 'recurrent depression' and others, but these have featured little in the literature on relapse.

While there has been little of use to clinicians from the large-scale epidemiological studies of relapse to depression, there has also been relatively little in the way of effective, theoretically informed therapeutic interventions to prevent relapse to depression (Clarke et al., in press). The majority of patients with depression are given anti-depressant medications and these are effective at preventing relapse so long as they are taken continually in the prescribed manner. However, even then they are not universally effective; there are clear problems with adherence partly due to unwanted side-effects and further problems with the continual cost of prescribing anti-depressants (Geddes et al., 2003). There have been several 'new dawns' for relapse prevention psychotherapies with first Interpersonal Psychotherapy (IPT) (e.g. Frank, Kupfer, Perel, & Cornes, 1990;

Weissman, Kasl, & Klerman, 1976), then Cognitive Behavioural Therapy (CBT) (e.g. Fava, Rafanelli, Conti & Belluardo, 1998), and more recently Mindfulness Based Cognitive Therapy (MBCT) (e.g. Teasdale, Segal, Williams, Ridgeway, Soulsby, & Lau, 2000) all proposed to provide a 'leap forward' in preventing depressive relapse. However, all three therapies have been found to be equivalent, having only a small-to-medium effect size and each reducing the relative risk of relapse by approximately 25% (Clarke et al., in press).

It can be argued that there has been very little overlap between the epidemiological studies and the trials of psychological theory-based therapeutic interventions. So, it could be that combining both the epidemiological, observable factors and the understanding of the psychologically-informed, latent factors may help us better understand the mechanisms behind relapse to depression and use this to inform the development and delivery of therapeutic interventions that may be able to deliver greater effectiveness at preventing relapse. This is not to contend that the therapies mentioned above were not produced on theoretical grounds with sound arguments for being effective at preventing relapse - they were - but these theories were arguably focussed only at the level of the unobservable/latent psychological factors without a grounding in the wider bio-psycho-social context of relapse to depression, which can be delivered only when accounting for the epidemiological and neuropsychological research literature too (Roiser, Elliot & Sahakian 2012). The prospective study was therefore conceived to focus on the combination of the epidemiologically defined risk factors, such as residual symptoms of depression, and one particular neuropsychologically proposed latent factor - cognitive control - in order to investigate risk for relapse to depression.

Context in which the Research Took Place

This research project was set-up and conducted in a context in which the National Health Service (NHS) faced (and continues to face) greater austerity than known in the sector perhaps since its inception in 1948 (Appleby, Crawford, & Emerson, 2008). Along with a

proposed £20bn of savings needed to be made across the sector (Department of Health (DoH), 2010), came changes in the commissioning of services (e.g. DoH, 2010; Walshe, 2010), and the need to provide greater evidence of cost-effectiveness and effectiveness of interventions by meeting nationally and locally defined Commissioning for Quality and Innovation (CQUIN) targets (NHS England, 2013). Given that IAPT services grew out of a policy document claiming that they could save the NHS and the government considerable sums of money by returning people with depression and anxiety back to work (Layard, Clark, Knapp, & Mayraz, 2007), such services are under greater pressure than most to deliver against these targets (Stolk, Hofman, Hafner, & Janta, 2014). As a result, conducting prospective studies in clinical settings, perhaps in particular in IAPT services, with the hope of delivering the necessary quality in order to give results sufficient credibility and utility, has become ever more difficult.

The present prospective study was set in an inner London Trust's IAPT services. Collectively these services have become somewhat of a centre of excellence for research in primary care mental health and subsequently there are many requests and demands on the services to facilitate, conduct and run research projects for a wide range and number of stakeholders.

In the context of a Doctorate in Clinical Psychology (D.Clin.Psy) course trainees are on placement three days a week and at University approximately one day a week whilst conducting the major research project. It is therefore a sizeable challenge to sufficiently project-manage the research at a local level within these time constraints, and this is made more difficult in settings where there are no additional resources free or available to facilitate this. Given the demands on the IAPT services listed above, no such resources were available for the present study. As a result, recruitment and data collection for the study had to be done by Psychological Wellbeing Practitioners (PWPs) who were already stretched by the need to meet their targets (IAPT, 2012) and by being asked to hold in mind

multiple research studies operating within the service simultaneously. Without the motivation and problem solving that comes from having an *in situ* research coordinator (Alvarez, 2013) it is not surprising that so few service users were recruited. Further, it was not possible (despite efforts) to negotiate a slightly lower weekly contact target for the PWPs so that they could have the necessary extra time to recruit for this study.

The difficulties with recruitment meant that whilst the prospective study aimed to include both three and six month follow-up appointments for each participant in order to prospectively gather data on relapse, this was not possible within the time-frame for the thesis. However, the study will continue to collect data up to 12 months post-treatment and the follow-up appointments will go ahead nonetheless.

Methodological Choices and Potential Difficulties

There were several difficult choices to make in the course of conducting the prospective study, all of which had potentially large implications for the study as a whole. Firstly, whilst cognitive control is usually and most reliably measured using experimental paradigms either with computer based tasks or in neuroimaging scanners (Nęcka, Sobczyk, & Śmieja, 2012), in order for measurement of cognitive control on the scale proposed for the prospective study to become feasible it was necessary to find a way of measuring it to fit with the current IAPT structure of sessions. At 'Step 2' sessions are only 30 minutes long including time for service users to complete the standard self-report measures. Therefore it was important that any means of measuring cognitive control to be utilised in the present study be short in length and simple to administer. As a standalone measure the Attentional Control Scale (ACS; Derryberry & Reed, 2002) is both adequately reliable and valid, but it was not designed to be used in mental health services or in settings such as the IAPT services where measures are repeated at every contact and often on a weekly basis (Derryberry & Reed, 2002). The ACS makes no reference to timescale in the instructions for the respondent and the wording of the items makes it such that a respondent might

consider it to refer to static, unchangeable states rather than transient experiences. The measure could be adapted by adding a phrase such as "over the last seven days..." in either the instructions to the respondent or as a prefix to each question. However, it has not been validated with such statements included, and so it was decided not to change the original structure of the ACS. It seems possible therefore that when completing the measure participants might have found it confusing to be given the measure repeatedly without some time related context. It may be the case that as they were completing symptom measures which have the instruction that respondents answer with reference to the last seven days only, when answering the ACS they assumed the same time scale applied. Equally, it could be the case that if participants were unsure of the applicable timescale and they asked the PWPs for advice, this may also have been the PWP's understanding. Either way there were changes in ACS scores for nearly all those that completed the measure, suggesting that this may not have caused much of a problem. It therefore proved feasible to use the ACS in this context and it may well be able to inform services about those that may be at greater risk of relapse in order to target them with alternative or additional interventions.

As discussed above, resources available for Doctorate in Clinical Psychology research projects are limited. This coupled with the ethical complications of paying/compensating participants for their time in research related to their own health-care meant that it was an easy decision to make not to pay participants, yet it was clearly a potentially costly one to the recruitment process (Church, 1993). A systematic review by Edwards and colleagues (2002) showed a doubling in the odds of response (albeit to postal surveys) when monetary incentives were offered for participation. In addition, this systematic review showed that questionnaires were more likely to be completed when coming from universities rather than from healthcare organisations (Edwards et al., 2002). As previously discussed it was not possible to have anyone other than the service user's

own PWP asking them for consent to participate in the present study. Therefore it may be that these contributed to the very low response-rate in the prospective study. However, some of the recommendations of Edwards and colleagues (2002) were able to be followed, such as choosing a brief questionnaire (rather than a longer one) and printing the questionnaires in colour.

No analysis of a large dataset is without its problems. One of the most surprising things to come out of conducting this research was that there appeared to be proportionally very few service users that returned to the services, therefore the number of relapsers was particularly small and certainly less than envisaged prior to starting the analyses. Some reasons as to why so few may have returned to the service are discussed in Part 2 of this thesis, though to briefly summarise: it may be the case that many service users were experiencing relapses after finishing treatment though were not being re-referred to the services due to personal choice or perhaps that their General Practitioners (GPs) (who are responsible for approximately 80% of all referrals to the IAPT services) had decided that as a relapse had occurred after treatment in IAPT, a different approach should be trialled next in the hope of preventing further relapses. This may therefore have led to such patients being referred elsewhere and so not returning to the IAPT services. As a result of having relatively few relapsers in the analyses the models built based on relapse were more susceptible to the impact of missing data than they might have otherwise been. One example of this is that the relationship between scores on the Generalized Anxiety Disorders scale (GAD-7) and relapse might have been unduly affected by missing data. It was decided that multiple imputation methods should not be used as despite having a large sub-set of the dataset with which to base the imputation on, it is possible that those with and without the GAD-7 scores represented different populations, so making any potential imputation invalid. However, using list-wise deletion to remove those with missing data from the analyses not only greatly reduced the power but also may have introduced

systematic selection bias, as those missing the data may have represented a different population of relapsers than those with recorded data on the GAD-7. This is particularly problematic as whilst non-systematic bias and a reduction in power may tend to bias results towards the null, a systematic bias could lead to erroneous conclusions in either direction (e.g. Kirkwood & Sterne, 2003). Therefore, in presenting the findings from the logistic regression models despite GAD-7 scores confounding the relationship between residual depressive symptoms and relapse for those with a recorded GAD-7 score, it was decided that models both with and without GAD-7 scores as a risk factor for relapse should be included. While this may have led to a somewhat greater difficulty in interpreting the findings in relation to relapse, it allowed for the consideration of the possibility that there are different patterns of risk factors across two potentially different sub-populations in the sample. As such, it highlighted an interesting and potentially new way of thinking about risk factors for relapse in a possibly distinct sub-population of service users presenting to primary care services with depression.

Conclusions

There have been many difficulties in conducting a prospective study in a clinical setting seeking to combine the investigation of factors at the observable and latent levels. Against the backdrop of austerity leading to reduced flexibility in contact targets for the PWPs recruiting and collecting data, and in the context of a D.Clin.Psy with few resources to project manage the research and the limitation in time allowed for the research to take place, the length of time taken to recruit participants and the number recruited led to an inability to collect data prospectively on relapse for a sufficient number of participants. The present study had to be reduced in scale and the aims adjusted accordingly, such that the focus of the prospective study was only on residual depressive symptoms as an outcome and not on relapse. However, despite all these difficulties the study was able to deliver results not previously found before, furthering knowledge about risk factors for residual

symptoms of depression and proving that there is utility in using self-report measures of cognitive control in primary care mental health services to consider service users risk of residual symptoms after treatment and therefore those most likely to relapse. With the continuation of the prospective study to collect data on relapse up to 12 months post-treatment, these findings can be extended and the conclusions drawn from the study can gain yet greater utility. The study made no attempt to improve the therapeutic interventions delivered to prevent relapse, but by contributing to a better understanding of the phenomenon it is hoped that even this modest D.Clin.Psy research project can lead to an improvement in the knowledgebase on relapse and potential advancements at the therapeutic level further into the future.

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Appendix I

Abstract of Literature Review in Format Outlined by PRISMA Guidelines.

Abstract

Objectives: To determine what factors confer risk for relapse to depression after acute phase treatment in adults and to consider the mechanisms by which they might operate.

Design: This study consisted of meta-reviews of systematic and non-systematic reviews of studies reporting on risk factors for relapse to depression in adults, and a systematic-review of neuroimaging and experimental studies investigating risk factors for relapse and potential mechanisms of action of these risk factors.

Data sources: Bibliographic databases: CAB Global Health Archive, Cochrane CENTRAL Trial Register, Cochrane Database of Reviews, Embase, International Pharmaceutical Abstracts, MEDLINE, Prospero, PsycEXTRA and PsycINFO, hand searching of reference lists and citations of included studies, and contact with experts in the field for unpublished reports.

Study eligibility criteria: We included studies that reported on at least one risk factor for relapse/recurrence to depression in adults 18 years old or above utilising a number of types of intervention. In Study 1 we included only systematic reviews of clinical trials, cohort studies or case-control studies which had reviewed studies that used well validated methods of determining depression onset/remission/recovery/relapse/recurrence. In Study 2 we included non-systematic reviews of any study designs, and in Study 3 we included neuroimaging and experimental studies that either had some longitudinal measurement of depressive symptoms over a minimum of eight weeks and used well validated methods of determining depressive onset/remission/recovery/relapse/recurrence, or that made cross-sectional comparisons between groups of remitted and relapsed/recurrently depressed participants determined by diagnosis from a psychiatrist or with a clinical interview.

Study appraisal and synthesis: To judge study quality in Study 1 the AMSTAR criteria along with items from PRISMA and the Cochrane Reviewer's Handbook were used, study quality was not assessed in Study 2, and in Study 3 criteria developed by Kmet, Lee and Cook (2004) were used to assess study quality. Each of the three stages of the present review involved a narrative synthesis with the formation of a matrix to consider each risk factor identified as associated with relapse/recurrence from the perspective of each reviewed study. Studies 2 and 3 included data on proposed mechanisms of action of the risk factors identified and these were used to derive a conceptual framework with which to consider directions for future research into relapse/recurrence to depression in adults.

Results: Only the presence of residual sub-threshold symptoms after acute phase treatment and the experience of some form of childhood maltreatment are well supported with strong evidence from high quality systematic reviews as risk factors for relapse to depression. There are a number of factors which to date had not previously been

systematically reviewed that these studies suggest play a role in conferring risk for relapse but which are not supported in the literature with the same degree of high quality evidence. These factors are: information processing and cognitive biases, reactions to stress and/or changes in mood, and persistent ruminative thinking in response to negative experiences, these may be brought about by dysfunction in neocortical and limbic structures (particularly the dmPFC and rACC) and dysfunction in the HPA axis and with REM sleep. Further, the studies have identified several potential mechanisms for the action of such risk factors and have considered the inter-relationships between these factors to propose a conceptual framework which may help guide future research into relapse/recurrence to depression.

Limitations: There was a paucity of high quality systematic reviews and very few that had the stated aim of identifying risk factors for relapse to depression. A large number of cohort studies and clinical trials identified in the literature searches were not included in the systematic and non-systematic reviews reviewed in Studies 1 and 2. Those that were included may have introduced various biases by using definitions of relapse and recurrence that result in the under-sampling of those that only ever have a single lifetime episode of depression, by suffering from high attrition rates, and by other inconsistencies across the studies in their inclusion and exclusion criteria.

Conclusions: Taken together these three studies have demonstrated that the consensus view of relapse may need amending, that there are no factors supported by studies able to provide the highest level of evidence for the prognosis or aetiology of a disease, conducted with high quality, providing strong evidence, which have utility in guiding the treating clinician in reducing their patient's risk of relapse/recurrence to depression. There are however a number of factors which to date had not previously been systematically reviewed that these studies suggest play a role in conferring risk for relapse. By considering the inter-relationships between these factors these studies were used to propose a conceptual framework which may be used to help guide future research into relapse/recurrence to depression in adults.

Implications of key findings: It may be that the current diagnostic systems impact the ability of researchers to identify risk factors for relapse to depression that have utility in the consulting room. However, irrespective of this, future studies would do best to investigate the relationships between cognitive and information processing (or affective) biases and relapse to depression to consider potential means by which these might be manipulated to reduce the risk of relapse for depressed patients.

Appendix II

List of Bibliographic Searches and Search Results from Literature Review

Searches	Results
CAB Global Health Archive 1910 to 1972	
1. (depression or Depressive disorder or Major depression or Unipolar depression or MDD).mp.	3255
2. (risk adj5 relapse).mp.	47
3. 1 and 2	1
4. (bipolar or bipolar disorder or manic depression).mp.	145
5. (alcohod abuse or drug abuse).mp.	290
6. (alcohol abuse or drug abuse).mp.	359
7. 4 or 6	504
8. 3 not 7	**1**
Cochrane CENTRAL Trial Register (searched on 16th November 2013)	
1. ("Depression" or "MDD" or "Unipolar" or "Depressive"):ti,ab,kw (Word variations have been searched)	29363
2. ("relapse" or "Recurrence" or "remission"):ti,ab,kw (Word variations have been searched)	41714
3. ("Bipolar" or "schizophrenia" or "psychosis" or "schizoaffective"):ti,ab,kw (Word variations have been searched)	12304
4. #1 and #2	293
5. #4 not #3	**282**
Cochrane Database of Reviews (searched on 16th November 2013)	
1. ("Depression" or "MDD" or "Unipolar" or "Depressive"):ti,ab,kw (Word variations have been searched)	95
2. ("relapse" or "Recurrence" or "remission"):ti,ab,kw (Word variations have been searched)	156
3. ("Bipolar" or "schizophrenia" or "psychosis" or "schizoaffective"):ti,ab,kw (Word variations have been searched)	31
4. #1 and #2	23
5. #4 not #3	**23**
Embase 1947 to 2013 Week 47	
1. exp recurrent brief depression/ or exp major depression/ or exp depression/ or exp long term depression/	323279
2. (depression or Depressive disorder or Major depression or Unipolar depression or MDD).mp.	460246
3. 1 or 2	486582
4. relapse.mp.	154579
5. recurrence.mp.	338066
6. 4 or 5	461682
7. 3 and 6	12839
8. (risk adj5 relapse).mp.	19560
9. 8 and 3	1444
10. ((relapse or recurrence) adj5 depressi*).mp.	4673
11. 9 or 10	5379
12. bipolar.mp.	77167
13. bipolar disorder/ or bipolar mania/ or bipolar depression/ or bipolar II disorder/ or bipolar I disorder/	40107
14. exp schizoaffective psychosis/	6134
15. alcohol abuse/	19526
16. drug abuse/	43593
17. 12 or 13 or 14 or 15 or 16	103069
18. 11 not 17	1068
19. ((risk or odds or chance or probability) adj5 relapse).mp.	20885
20. 3 and 19	1538
21. 11 or 20	5417
22. 21 not 17	**1150**
Embase 1947 to 2013 Week 47 Search for Review Articles Only	
1. exp recurrent brief depression/ or exp major depression/ or exp depression/ or exp long term depression/	323279
2. (depression or Depressive disorder or Major depression or Unipolar depression or MDD).mp.	460246
3. 1 or 2	486582
4. relapse.mp.	154579
5. recurrence.mp.	338066
6. 4 or 5	461682
7. 3 and 6	12839
8. (risk adj5 relapse).mp.	19560
9. 8 and 3	1444
10. ((relapse or recurrence) adj5 depressi*).mp.	4673
11. 9 or 10	5379
12. bipolar.mp.	77167
13. bipolar disorder/ or bipolar mania/ or bipolar depression/ or bipolar II disorder/ or bipolar I disorder/	40107
14. exp schizoaffective psychosis/	6134
15. alcohol abuse/	19526
16. drug abuse/	43593
17. 12 or 13 or 14 or 15 or 16	103069
18. 11 not 17	1068
19. ((risk or odds or chance or probability) adj5 relapse).mp.	20885
20. 3 and 19	1538

21. 11 or 20	5417
22. 21 not 17	1150
23. systematic review.mp. or "systematic review"/	98424
24. meta analysis.mp.	115569
25. literature review.mp.	55934
26. 23 or 24 or 5	221228
27. 22 and 26	**77**

International Pharmaceutical Abstracts

1. (depression or Depressive disorder or Major depression or Unipolar depression or MDD).mp.	8151
2. (risk adj5 relapse).mp.	276
3. 1 and 2	38
4. (bipolar or bipolar disorder or manic depression).mp.	1426
5. (alcohol abuse or drug abuse).mp.	6685
6. (alcohol abuse or drug abuse).mp.	6865
7. 4 or 6	8239
8. 3 not 7	**31**

Ovid MEDLINE 1946 to November Week 3 2013

1. exp major depression/ or exp "depression (emotion)"/	73699
2. ((relapse or recurrence) adj5 depressi*).mp.	1406
3. bipolar disorder/ or affective psychosis/ or mania/	30705
4. exp Schizoaffective Disorder/	37751
5. 3 or 4	65458
6. exp Depressive Disorder, Major/	18234
7. exp Depressive Disorder, Major/ or exp Depressive Disorder/ or exp Depression/	148814
8. 2 or 7	149074
9. Bipolar Disorder/	30705
10. 8 not 9	139693
11. Child/	1339552
12. 10 not 11	129087
13. 2 and 7	1146
14. 13 not 19	1054
15. 14 not 11	1001
16. Substance-Related Disorders/	76481
17. 15 not 16	**990**

Ovid MEDLINE 1946 to November Week 3 2013 Search for Review Articles Only

1. exp major depression/ or exp "depression (emotion)"/	73699
2. ((relapse or recurrence) adj5 depressi*).mp.	1406
3. bipolar disorder/ or affective psychosis/ or mania/	30705
4. exp Schizoaffective Disorder/	37751
5. 3 or 4	65458
6. exp Depressive Disorder, Major/	18234
7. exp Depressive Disorder, Major/ or exp Depressive Disorder/ or exp Depression/	148814
8. 2 or 7	149074
9. Bipolar Disorder/	30705
10. 8 not 9	139693
11. Child/	1339552
12. 10 not 11	129087
13. 2 and 7	1146
14. 13 not 19	1054
15. 14 not 11	1001
16. Substance-Related Disorders/	76481
17. 15 not 16	990
18. Systematic review.mp	37815
19. literature review.mp	38952
20. meta analysis.mp	67893
21. 18 or 19 or 20	127903
22. 17 and 21	**33**

PsycEXTRA 1908 to November 16, 2013

1. exp Postpartum Depression/ or exp Recurrent Depression/ or exp Atypical Depression/ or exp Endogenous Depression/ or exp Reactive Depression/ or exp Treatment Resistant Depression/ or exp Major Depression/	4479
2. (risk adj5 relapse).mp.	55
3. 1 and 2	9
4. exp Bipolar Disorder/ or exp Mania/	729
5. mental health/	6267
6. exp Alcohols/	393
7. exp Alcohol Abuse/	3771
8. exp Drug Abuse/	12931

9. 7 or 8	12931
10. 4 or 9	13625
11. 3 not 10	**9**
Prospero (searched on 16th November 2013)	
"Depression" OR "Depressive" OR "MDD" OR "Unipolar". In all fields.	**227**
PsycINFO 1806 to November Week 3 2013	
1. exp major depression/ or exp "depression (emotion)"/	111027
2. recurrent depression/	617
3. exp Relapse Prevention/ or exp "Relapse (Disorders)"/	6945
4. 1 or 2	111027
5. ((relapse or recurrence) adj5 depressi*).mp.	1939
6. 3 and 4	1133
7. 6 or 5	2229
8. 7	2229
9. limit 8 to (human and English language and journal article)	1598
10. bipolar disorder/ or affective psychosis/ or mania/	21943
11. exp Schizoaffective Disorder/	2568
12. 10 or 11	24023
13. 9 not 12	1382
14. exp Child Psychopathology/	1426
15. 13 not 14	1381
Substance abuse.mp	27069
exp Drug Abuse/	85848
exp Alcohol Abuse/	38362
16 or 17 or 18	85848
15 not 19	**1320**
PsycINFO Search for Review Articles Only	
exp major depression/ or exp "depression (emotion)"/	110021
(depression or Depressive disorder or Major depression or Unipolar depression or MDD).mp.	213339
recurrent depression/	613
1 or 2 or 3	213628
relapse.mp.	17745
recurrence.mp.	5591
exp Relapse Prevention/ or exp "Relapse (Disorders)"/	6898
5 or 6 or 7	22074
4 and 8	5177
exp "Literature Review"/ or exp Meta Analysis/	25128
systematic review.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]	8537
meta analysis.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]	14296
10 or 11 or 12	42663
9 and 13	192
exp Bipolar Disorder/	18849
exp Alcohol Abuse/	38107
exp Drug Abuse/	85184
exp Drug Addiction/	11194
15 or 16 or 17 or 18	103406
14 not 19	161
((relapse or recurrence) adj5 depressi*).mp.	1920
20 and 21	**52**

Appendix III

Additional Details Extracted From Each Reviewed Study in Literature Review

Study 1:

Reviewed Studies	Databases searched and years included	Search terms	Inclusion Criteria	Exclusion Criteria
Beshai et al., 2011	PsycINFO and PubMed years not stated	keywords only: "relapse", "recurrence", "prevention", "depression", "cognition", "mindfulness", "interpersonal" AND "therapy"	a) adult participants (18 or over), b) employing some form of psychotherapy, c) psychotherapy used as a standalone procedure targeting relapse/recurrence prevention d) used either a treatment or non-treatment control group	None Stated
Clarke et al., in press	CENTRAL, Embase, Medline, and PsycINFO and PROQUEST from beginning of databases to 2012	Keywords and MeSH terms: depression' and 'long-term/ relapse/recurrence' using a highly sensitive RCT filter	Randomised controlled trials of non-pharmacological interventions were included if participants were adults who had experienced an episode of major depression and partially or fully recovered. There was a minimum follow-up period of 12-months from the start of the intervention.	None Stated
Feng et al., 2012	Cochrane Library, EBSCO Host, Medline OVID, ProQuest Medical Library, and PubMed, all 2000-2010, hand searching.	Keyword and MeSH terms: group therapy, cognitive therapy, cognitive behavioural therapy, CBGT, psychotherapy, depression, relapse, and recurrence	Participants diagnosed using: ICD-10, DSM-III/IIIR/IV/IV-TR or RDC, were over 18 years old and could be any gender or race; RCT design with at least one group undergoing CBGT; written in English; results presented on level of depression and relapse rate; and studies had sufficient data to calculate effect size.	CBGT taking place over the phone or the Internet.
Hardeveld et al., 2010	PsycINFO and Medline, plus hand searching of references. All searched January 1980-August 2008	Keywords only: 'Recur*', 'Relaps*', 'Depress*', 'Predict*' and 'course'.	English Language, adult population only; naturalistic cohort studies of subjects with MDD diagnosed by interview of checklist based on RDC/BCC, DSM-III/III-R/IV or ICD-9/10; course measured by standardised instrument/checklist, minimum follow-up 6 months, at least 50 participants, criteria of remission/recovery/relapse/recurrence according to Frank et al 1991 criteria.	Bi-polar, SAD, Post-partum depression, studies including specific age groups only.
Hughes & Cohen, 2009	Medline, PsycINFO, Embase, Cochrane Library, all 1988-2008, hand searching.	Keyword and MeSH terms: Given in tables for each database.	1) Follow-up period of 10+ years 2) adults over 18 3) at least 1 group with unipolar depressive disorder, 4) description of ADM treatment 5) at least 1 clinical or psychosocial outcome, excluding suicide or mortality, 6) Published in English. Same inclusion criteria for studies of nondrug treated individuals, but statement that participants had not received ADMs.	Studies that examined only suicide or mortality .
Kok et al., 2013	PubMed, Embase, PsycINFO. Searched from beginning of databases to 4th December 2012.	Keyword and MeSH terms: 'depression or depressive disorder or major depression were combined with heart diseases or gastrointestinal diseases or diabetes mellitus or arthritis, rheumatoid or asthma or HIV or neoplasms and incidence or follow-up studies or prognos* or predict* or course or outcome or relaps* or recur* or remis* or epidemiology.	In English, Dutch, Spanish, Polish or German. (1) longitudinal measurement of course of depression (2) numbers or percentages of recurrence presented a) diagnosis with interview or questionnaires based on DSM-III/III-R/IV (3) follow-up of 6+ months (4) data collected on patients with and without chronic somatic illnesses assessed via self-report, medical records or by a medical professional.	Bi-polar disorder
Nanni et al., 2011	Medline, PsycINFO, and Embase. Searched from beginning of the databases to December 2010	Keywords: child*maltreatment, child*abuse, child* neglect, early experience. depress*, mood disorder, MDD, recurrence, persistence, chronic, duration, length, improvement, response, remission, treatment, psychotherapy, CBT, pharmacotherapy, antidepressant, SSRI	Childhood maltreatment including physical abuse, sexual abuse, neglect, or family conflict or violence); depressive disorder in population-based or clinical samples; and evaluation with relevant depressive symptom measures, written in English.	Animal studies; articles not published in English

Study 2:

Reviewed Studies	Databases searched	Years included	Type of searching	Search terms	Inclusion Criteria	Exclusion Criteria	Number of included studies
Beckerman & Corbett,2010	None stated	N/A	None stated	None stated	Not Stated	Not Stated	Not stated
Belsher & Costello, 1988	None stated	N/A	None stated	None stated	Not Stated	Not Stated	Not stated
Burcusa & Iacono, 2007	PSYCINFO and Science Citation Index Expanded. Hand searching	Not stated	Keywords	"Recurrence" "Recurrent" "depression" "risk" "correlate"	Not Stated	Not Stated	51
Costa e Silva, 2004	None stated	N/A	None stated	None stated	Not Stated	Not Stated	Not stated
de Carvalho et al., 2011	None stated	N/A	None stated	None stated	Not Stated	Not Stated	Not stated
Hammen, 2003	None stated	N/A	None stated	None stated	Not Stated	Not Stated	Not stated
Hick & Chan, 2010	None stated	N/A	None stated	None stated	Not Stated	Not Stated	Not stated
Hollon & DeRubeis, 2009	None stated	N/A	None stated	None stated	Not Stated	Not Stated	Not stated
Keller, 1996	None stated	N/A	N/A	N/A	N/A	N/A	N/A
Kerr et al., 2013	None stated	N/A	None stated	None stated	Not Stated	Not Stated	Not stated
Kessler, 1997	None stated	N/A	None stated	None stated	Not Stated	Not Stated	Not stated
Lau et al., 2004	None stated	N/A	None stated	None stated	Not Stated	Not Stated	Not stated
Liu, 2013	None stated	N/A	None stated	None stated	Not Stated	Not Stated	Not stated
Modell & Lauer, 2007	None stated	N/A	None stated	None stated	Not Stated	Not Stated	Not stated
Monroe & Harkness, 2005	None stated	N/A	None stated	None stated	Not Stated	Not Stated	Not stated
Palagini et al., 2013	None stated	N/A	None stated	None stated	Not Stated	Not Stated	Not stated
Robinson & Sahakian, 2008	None stated	N/A	None stated	None stated	Not Stated	Not Stated	Not stated
Scher et al., 2005	None stated	N/A	N/A	N/A	N/A	Not Stated	30
Scott, 2001	None stated	N/A	None stated	None stated	Not Stated	Not Stated	Not stated
Segal et al., 1996	None stated	N/A	None stated	None stated	Not Stated	Not Stated	Not stated
Sipe & Eisendrath, 2012	None stated	N/A	None stated	None stated	Not Stated	Not Stated	Not stated

Study 3:

Reviewed Studies	Inclusion Criteria	Exclusion Criteria	How Sample Recruited
Anderson et al., 2011	aged 18–60, in good physical health. Control group with no personal history of psychiatric disorder or a family history of treated depression; currently depressed participants met criteria for MDE; and remitted depressed group were in full remission with no current psychiatric disorder, a history of at least two prior MDEs (one lasting at least 2 months) and a MADRS score < 13.	Current/past physical illness or disability; current alcohol or drug dependence/harmful use; history of bipolar affective disorder, psychosis, dementia or mental impairment; taking psychoactive medications (apart from ADM, antipsychotics or lithium). Anxiety disorders not pre-dating diagnosis of MDD.	From Larger sample of 2004 Primary Care Patients in 2 UK centres supplemented with psychiatric outpatients with history of depression
Chopra et al., 2008	Not Stated	Not Stated	Phase 1: 301 patients with MDD were randomized to receive CBT or ADM. Phase 2: participants who remitted underwent mood provocation protocol and followed-up for 18 months.
Dai & Feng, 2011	Chinese-speaking adults aged 18-40. NCs: score of <5 on BDI and BAI, and no history of depressive disorder or other psychological disturbance from SCID. For RMD: scoring <8 on HRSD and at least two previous MDEs, most recent onset at least 8 weeks ago. MDD group: scoring 20+ on the HRSD and diagnosis from psychiatrist according to the DSM-IV criteria.	Severe head trauma and learning disabilities, current or lifetime psychotic symptoms, bipolar disorder and alcohol or substance abuse within the past 6 months. All participants had normal or rectified eyesight with no colour blindness, and were right-handed.	NC Group: Participants recruited via advertising on university bulletin boards. RMD Group: recruited through psychotherapists, and were screened to determine recovery status according to the DSM-IV criteria. MDD Group: recruited through psychiatrists
Franck et al., 2007	Currently depressed group: DSM-IV diagnosis of MDD, HRSD score of 13+ and BDI score 20+. Formerly Depressed: past diagnosis of MDD given by a psychiatrist/clinical psychologist, received ADM or psychotherapy during the episodes, symptom free for at least one month. HRSD score <13 and BDI-II <20. Never depressed: screened with the MINI and included if they reported no prior history of depression. HRSD score <13 and a BDI-II <20.	For Never Depressed: any past psychological disorder based on self-report questionnaire.	Currently depressed were recruited from psychiatric hospitals in Belgium. Formerly depressed and never depressed recruited using media advertisements in Belgium. All participants were financially compensated for their participation in the study.
Huffziger & Kuehner, 2009	MDD single or recurrent episode, and Dysthymic Disorder according to ICD-10 at index admission	Not stated	3.5 year follow-up assessment, of,patients originally recruited during their inpatient treatment at the Central Institute of Mental Health in Mannheim, Germany
Lethbridge & Allen, 2008	Meeting DSM-IV-TR criteria for 1+ previous episodes of MDD.	Current depression within 10 weeks of first testing session. History of psychosis or bi-polar disorder. Inability to speak English, and/or inability to provide informed consent.	Recruited via advertisements placed around the University of Melbourne, in the Herald Sun newspaper, and via email newsletters to post-graduates at the University.
Moreno et al., 2000	Not Stated	Not Stated	methods described in a previous report detailing the acute mood response to TRP depletion (Moreno et al 1999).

Morris et al., 2012	Remitted Depressed group: past diagnosis of MDD according to DSM-IV criteria assessed with the SCID-I.	Current MDD, past bi-polar disorder, PTSD or health conditions known to influence HPA function and non-prescription drugs that can affect cortisol levels.	Recruited from graduate and undergraduate programs at Vanderbilt University.
Nixon et al., 2013	2+ previous episodes MDD diagnosed with SCID, currently in sustained remission/recovery with normalized function for 3+ months and a HAM-D score <8.	co-morbid Axis I psychiatric disorder; personality disorder; drug/alcohol disorder; untreated medical disorder; any previous or current central nervous system disease; or fMRI safety issues. Controls were excluded if there was evidence of current or past psychiatric disorder.	Recruited via referral from general adult psychiatric clinics in Nottingham, UK. Controls recruited via posters displayed at a General Hospital and a community surgery in Nottingham.
O'Brien-Simpson et al., 2009	Previous MDD, but did not meet criteria for diagnosis of MDD at the time of testing.	Drug or alcohol abuse or dependence, history of brain injury or central nervous system disease.	Not stated
Risch et al., 2010	DSM-IV criteria for MDD or recurrent MDD, currently in remission.	Depression with psychotic symptoms, bipolar disorder, PTSD, organic psychiatric disorders, substance-abuse related disorders, schizophrenia, schizoaffective disorders, borderline personality disorder, or acute suicidality. RD patients: >18 on BDI. ND: no current or past depression.	Recruited from the outpatient psychiatric clinics of the Friedrich Schiller University of Jena and the Sophien and Hufeland Clinic of Weimar, Germany.
Sears et al., 2011	Previously depressed group: 1+ episode of MDD over past 2 years and BDI score <7. Never depressed group: BDI scores <7 and no history of MDD during past 2 years. Dysphoric group: BDI scores > 19, classified as ''previously depressed'' based on their responses on the self-report inventory.	Previously depressed group: experiencing depressive symptoms at time of testing, male gender.	Recruited via an online research participation system for undergraduates at University of Calgary and through campus advertisements. Participated in exchange for extra course credit or $20.00 (CAN).
Segal et al., 1999	All participants were between the ages of 18 and 65 years old, met minimum eighth-grade education requirement or were able to complete assessment instruments unassisted, and spoke English as their primary language. Only chose if their most recent episode of depression met criteria for a primary diagnosis of MDD.	a) Current diagnosis of bipolar affective disorder, substance abuse disorder, or schizophrenia, and b) a trial of ECT within the past 6 months. `	From one of two outpatient clinics offered through the Clarke Institute of Psychiatry's Mood and Anxiety Disorder Division and the Depression Clinic.
Segal et al., 2006	Diagnosis of MDD according to DSM-IV, aged 18-65 years, minimum eighth-grade education, able to read English and to provide informed consent. Post-treatment evaluations were based LIFE interview and HDRS-17. Remission was defined as minimal symptoms for a12+ weeks, no longer meeting diagnostic criteria for MDE, and a HDRS-17 score < 11. These were used to determine eligibility for the mood provocation phase of the study.	(1) Current diagnosis of bipolar disorder, substance abuse disorder, schizophrenia, or borderline personality disorder, (2) a trial of electroconvulsive therapy within the past 6 months, and (3) a score of <12 on HDRS.	Recruited by referrals from the Mood and Anxiety Disorders Program at the Centre for Addiction and Mental Health or from media announcements.
Watkins & Baracaia, 2002	Aged 18-65 years old. Currently depressed: met criteria for MDD on SCID and score 16+ on the BDI. Recovered Depressed: did not meet criteria for current MDE on SCID, 1+ previous episodes, scored <15 on BDI. Never Depressed did not meet criteria for any past or current diagnosis of MDE on the SCID and scored <15 on the BDI	None stated	Currently depressed: recruited from both inpatient and outpatient settings. Recovered Depressed: recruited from a self-help charity for depression. Never Depressed: no comment on method of recuitment.

Appendix IV

Details of Studies Excluded From the Literature Review

Study 1.

Study Citation	Comments on Inclusion	Study design of included studies	Study population	Type of Intervention	Comparisons of relevance to relapse	How outcomes recorded	Main Results
Bourgon & Kellner, 2000. The Journal of ECT. Vol.16(1), Mar 2000, pp. 19-31.	Doesn't state how relapse is measured in included studies.	Intervention studies using ECT	Current Major Depression only	ECT	relapsers vs non-relapsers	Relapse recorded but not stated how.	The only reported predictive symptom was the presence of delusions. Medication resistance before ECT was the also reported as predicting relapse. The DST and TRH tests were considered as biological markers that could predict relapse.
Santos, et al.,2013. Clinical Practice & Epidemiology in Mental Health, 2013, 9, 221-237	No data on factors related to relapse despite statements about them.	The studies were RCTs, prospective cohorts, cross-sectional studies and case-control studies	no limitation of age, young women with depression or not	positive psychology strategies or emotion in evaluating patients with depression or not.	Some articles compared these interventions to controlled groups by the symptoms of depression and the scores of depression scales	Self-report measures of: depression, positive and negative affect, gratitude, hope, stress, resilience, life satisfaction, self-esteem, automatic thoughts, happiness, and meaning and mindfulness.	Positive psychology interventions were reported to impact depressive symptoms as well as resilience and coping abilities to reduce relapses.
Oestergaard & Moldrup, 2011. Journal of Affective Disorders. Vol.131(1-3), Jun 2011, pp. 24-36.	Nothing on mechanism/predictors of relapse	Studies included RCTs of combined psychotherapy and ADM vs ADM alone .	people with MDD of any age	ADM and psychotherapy.	relapsers vs non-relapsers	Remission and relapse rates from self-report measures, in particular HAM-D	ADM patients had higher risk of relapse up to 12 months after treatment.
Vittengl, Clark, Dunn, & Jarrett 2007. Journal of Consulting & Clinical Psychology. 75(3):475-88, 2007 Jun.	Nothing on mechanism/predictors of relapse	RCTs	Adults 18+ with MDD	CT or CBT	relapsers vs non-relapsers	Mostly DSM criteria using HRSD, or diagnosed in outpatient settings.	Approximately half of all responders to A-CT relapse within 2 years if not receiving continuation-phase treatment. A-CT reduces relapse relative to ADM whether continued in conjunction with ADM or not. C-CT reduces risk of relapse compared with no treatment conditions, and or compared with ADM.
Cuijpers, et al., 2013. BMJ Open 2013;3:e002542. doi:10.1136/bmjopen-2012-002542	Nothing on mechanism/predictors of relapse	RCTs	Adults with MDD	CBT	Not stated	HAM-D	There was a non-significant trend towards acute phase CBT patients having lower risk of relapse than acute phase ADM patients.
Geddes, et al., 2003. Lancet. 361(9358): p 653-661. 2003.	Nothing on mechanism/predictors of relapse	RCTs	Adults with MDD	ADM	Proportions relapsing in each trial arm, relapsers vs non-relapsers	Mostly DSM/RCD criteria	Meta-analysis results revealed that continuation ADM reduced the risk of relapse.
Chiesa & Serretti 2011. Psychiatry Research 187 (2011) 441–453	Nothing directly on mechanism/predictors of relapse but some tentative statements about things hypothesised to be related to relapse	RCTs	Adults with psychiatric disorders	MBCT	Differences in relapse rate between groups, pre-post BDI scores, scores in remitted vs non-remitted	Differences in 1-year relapse and recurrence rates in patients suffering from MDD assigned to MBCT or to a control group	Only one study found that MBCT was comparable to established treatment options. Reported that MBCT had an additive effect to usual care for reducing residual symptoms.

Study 2.

Study Citation	Comments on Inclusion	Study design of included studies	Study population	Comparisons of relevance to relapse	How outcomes recorded	Main Results
Alexopoulos,Young, Abrams, Meyers & Shamoian, 1989. Biological Psychiatry. Vol.26(6), Oct 1989, pp. 551-564.	Geriatric Depression only		Mixed age adults with depression	relapsers vs non-relapsers		History of 3+ episodes was the strongest clinical or demographic predictor time to relapse. However recent studies have not found this to be the case but these studies did separate relapse from chronicity of depression.
Arean& Reynolds, 2005. Biological Psychiatry. 58(4):277-82, 2005 Aug 15.	Geriatric Depression only	A mixture of cohort studies, trials, and cross-sectional studies, and others	Mostly older adults	Not stated	Not stated	
Auerbach, Webb, Gardiner & Pechtel, 2013. Journal of Psychotherapy Integration. Vol.23(3), Sep 2013, pp. 222-235.	Nothing directly on relapse.	Mostly neuroimaging and experimental designs	Mostly adults, some child and adolescent	Depressed Vs healthy controls or cognitively vulnerable	Mostly areas of activation on neuroimaging	Findings suggest that depressed individuals spend more time attending to depressogenic stimuli which exacerbates negative affect and likely, maintains depressive symptoms. Such attentional and information processing biases are central components of the cognitive model of depression, which likely fuel other higher-order components of the model (negative core beliefs about the self).
Disner, Beevers, Haigh & Beck, 2011. Nature Reviews Neuroscience, 2011, 12, 467-477	Nothing directly on relapse.	Neuroimaging studies	mainly adutls with depression	mainly adults with depression compared to healthy adults	areas of neural activation	The authors suggest that amygdala hyperactivity, hypoactivity in the DLPFC and blunted nucleus accumbens response in depressed individuals increase the salience of negative stimuli and decrease the salience of positive or rewarding stimuli leading to the common cognitive biases towards negatively valenced information and away from positively valenced information, thus maintaining depressed mood.
Driessen, & Hollon, 2010. Psychiatric Clinics of North America. Vol.33(3), Sep 2010, pp. 537-555.	Nothing on mechanism/predictors of relapse	Trials	adults with depression or recurrent depression	relapsers vs non-relapsers	mostly SCID or interviews	
Hemmeter, Hemmeter-Spernal & Jurgen-Christian, 2010. Expert Review of Neurotherapeutics. Vol.10(7), Jul 2010, pp. 1101-1115.	Nothing on mechanism/predictors of relapse	Intervention studies using sleep deprivation; some neuroimaging studies	Adults with severe depression	mostly responders vs non-responders	self-report symptoms and/or clinical interviews	Men and women respond equally well. Neither age, number of hospitalizations, earlier treatments, duration of episode or severity of depression appear consistently related to responsiveness to SD.
Trew, 2011. Clinical Psychology Review. Vol.31(7), Nov 2011, pp. 1156-1168.	Nothing on mechanism/predictors of relapse	Neuroimaging, experimental studies using behavioural paradigms	Adults with depression	Some healthy controls		BAS sensitivity was a predictor of depressive symptoms, duration of depression, general functioning, and time to recovery and positively predicts clinical improvement at six and eight months. Actual-ideal discrepanciesweare also associated with depression, suggesting approach deficits impact upon depression.

Bunney & Bunney, 2013. Biological Psychiatry. Vol.73(12), Jun 2013, pp. 1164-1171.	Nothing on mechanism/ predictors of relapse				
Coyne & Whiffen, 1995. Psychological Bulletin. Vol.118(3), Nov 1995, pp. 358-378.	Nothing on mechanism/ predictors of relapse				
Dimidjian & Davis, 2009. Current Psychiatry Reports. 11(6):453-8, 2009 Dec.	Nothing on mechanism/ predictors of relapse				
Hammen, 2006. Journal of Clinical Psychology. 2(9):1065-82, 2006 Sep.	Nothing on mechanism/ predictors of relapse				
Joffe & Cohen, 1998. Biological Psychiatry. Vol.44(9), Nov 1998, pp. 798-811.	Nothing on mechanism/predictors of relapse	Multiple types including cohorts of healthy and depressed individuals, experimental studies and trials.	Mostly adult women with depression	Mostly adult women without depression/healthy controls	A history of postpartum major depression and psychotic mania confers increased for relapse after subsequent pregnancies.
Teasdale, 1999. Behaviour Research and Therapy. Vol.37(Suppl 1), Jul 1999, pp. S53-S77.	Nothing on mechanism/ predictors of relapse				

Study 3:

Study Citation	Comments on Inclusion	Study population	Type of Intervention	Comparisons of relevance to relapse	How outcomes recorded	Main Results
Kronmuller et al., 2008. British Journal of Psychiatry. 192(6):472-3, 2008 Jun	Nothing on mechanism/predictors of relapse	Currently depressed adults.	Main investigations were carried out at the beginning of treatment, at discharge from hospital as well as 1 and 2 years after discharge.	Currently depressed vs healthy Controls. Remitted Vs Non-Remitted. Recurrently depressed vs Non-recurrence.	Relapse was defined according to DSM–IV criteria for MDD, and the LIFE was used. MRI scans of the whole brain were also obtained .	Males but not females with a recurrence of depression had smaller hippocampal volumes.
Frodl et al., 2003.Biological Psychiatry 53(4),338–344	Nothing on mechanism/predictors of relapse	Adults in three groups: first episode depressed, recurrent depressed, and healthy controls.	MRI images taken in scanner	First episode depressed vs recurrent Depressed vs healthy Controls	Amygdala volume was measured.	Recurrent depressed patients had smaller left and right amygdala volumes compared to first episode depressed patients.
Nandrino, J-L., Dodin, V., Martin, P., Henniaux, M. 2004. Journal of Psychiatric Research 38 (2004) 475–484	Not reporting on explanatory factors, just describing a difference between recurrently and first episode depressed patients.	First episode depressed and recurrently depressed adults.	Visual counting task: subjects count occurrence of words with positive, negative, or neutral affective valence, taken from a French current word list. Asked to focus attention in a first experimental condition on negative, then in a second condition, on positive words.	First-episode major depressive patients vs recurrent depressed patients	Brain electrical activity was recorded from Fz (frontal), Cz (central), and Pz (parietal) electrodes. Vertical eye movements were recorded.	After clinical improvement at 28 day follow-up there were no amplitude differences between the groups in the negative attention condition but groups differed in P300 amplitudes elicited by negative, neutral and positive words with first-episode patients having lower amplitudes than controls, and recurrent patients.
Nandrino, J-L., Pezard, L., Posté, A., Réveillère, C., & Beaune, D. 2002. Psychopathology 2002;35:335–340	No explanatory factor/ predictor of relapse/ recurrence just description of factor that is increased in recurrently depressed patients.					
Frodl et al., 2004. J Clin Psychiatry 2004; 65: 492–9.	No use of clinical interview or measures for depressive symptoms/history; hospital records checked only.					
Georgiadi E, Liotti M, Nixon NL, Liddle PF, 2011. Psychophysiology 48(9),1192–1201	Nothing on explanatory factors for relapse, more a noted difference between remitted and acutely depressed.	First experimental group: adults with remitted MDD defined by DSM-IV criteria, and age-and gender matched healthy control participants. Second experimental group: Adult patients meeting criteria for current MDD and age and gender-matched healthy controls	Go/no-go paradigm. Participants asked to press a button for go stimuli and avoid pressing it for no go stimuli. Participants were asked to respond quickly and accurately with the word ‘‘TIME’’ appearing on screen if response came after 450ms after stimulus onset.	Remitted depressed vs matched controls and currently depressed vs matched controls.	Electrical brain activity was recorded from 128 tin electrodes distributed over the whole scalp. Eye movements were monitored by four external electrodes, two at the corner of the eyes (for horizontal eye movements) and two below the eyes (for vertical eye movements).	Remitted patients had higher ERN amplitudes relative to the matched controls and current MDD patients. Current depressed patients did not have different amplitudes from their matched controls. Younger remitted patients had the greatest ERN.

Appendix V

List of Studies Excluded From Literature Review

First Author	Title	Citation
Aaron S.D.	Outpatient oral prednisone after emergency treatment of chronic obstructive pulmonary disease.	New England Journal of Medicine. 348 (26) (pp 2618-2625), 2003.
Abdel-Baki A.	Pharmacotherapy challenges in patients with first-episode psychosis.	Journal of Affective Disorders. 138 (SUPPL.) (pp S3-S14), 2012. Date of
Abraham	Clinical Outcome and Memory Function With Maintenance Electroconvulsive Therapy: A Retrospective Study. [References].	The Journal of ECT. Vol.22(1), 2006, pp. 43-45.
Abulseoud O.A.	A retrospective study of gender differences in depressive symptoms and risk of relapse in patients with alcohol dependence.	American Journal on Addictions. 22 (5) (pp 437-442), 2013.
Addington, D. E	Attempted suicide and depression in schizophrenia.	Acta Psychiatrica Scandinavica. Vol.85(4), Apr 1992, pp. 288-291.
Addington,	Depression in people with first-episode schizophrenia.	The British Journal of Psychiatry. Vol.172(Suppl 33), Jun 1998, pp. 90-
Afzali H.H.A.	A critical review of model-based economic studies of depression: Modelling techniques, model structure and data sources.	PharmacoEconomics. 30 (6) (pp 461-482), 2012. Date of Publication: 2012.
Agosti V	One year clinical and psychosocial outcomes of early-onset chronic depression.	Journal of Affective Disorders. 54(1-2):171-5, 1999 Jul.
Akister, Jane	Protecting children through supporting parents.	Journal of Public Mental Health. Vol.8(4), Dec 2009, pp. 11-17.
Alexopoulos G.S.	Does vascular disease cause late-life depression?.	Economics of Neuroscience. 3(7), 49-56. 2001.
Alexopoulos G.S.	Comorbidity of late life depression: An opportunity for research on mechanisms and treatment.	Biological Psychiatry. 52 (6) (pp 543-558), 2002. Date of
Alexopoulos GS	Outcomes of geriatric depression.	Clinics in Geriatric Medicine. 8(2):363-76, 1992 May.
Ali NS	Effectiveness of counselling for anxiety and depression in mothers of children ages 0-30 months by community workers in Karachi, Pakistan: a quasi experimental study	BMC Psychiatry. 10:57, 2010.
Allen N.B.	Early intervention for depressive disorders in young people: the opportunity and the (lack of) evidence.	The Medical journal of Australia. 187 (7 Suppl) (pp S15-17), 2007.
Allen S.S.	Menstrual phase and depressive symptoms differences in physiological response to nicotine following acute smoking	Nicotine and Tobacco Research. 15 (6) (pp 1091-1098), 2013. Date of
Allen	Postpartum depressive symptoms and smoking relapse.	American Journal of Preventive Medicine. Vol.36(1), Jan 2009, pp.
Allsop S.	The process of relapse in severely dependent male problem drinkers.	Addiction. 95 (1) (pp 95-106), 2000. Date of Publication: 2000.
Almeida OP	Cardiovascular diseases do not influence the mental health outcome of older men with depression over 6 years.	Journal of Affective Disorders. 144(3):248-52, 2013 Jan 25.
Alnaes, R Torgersen, S	Personality and personality disorders predict development and relapses of major depression.	Acta Psychiatrica Scandinavica. Vol.95(4), Apr 1997, pp. 336-342.
Altamura A.C.	Rethinking the role of long-acting atypical antipsychotics in the community setting.	International Clinical Psychopharmacology. 27 (6) (pp
Altemus M	Phenotypic differences between pregnancy-onset and postpartum-onset major depressive disorder.	Journal of Clinical Psychiatry. 73(12):e1485-91, 2012 Dec.
Alvarez-Uria G.	Factors associated with treatment failure of patients with psychiatric diseases and injecting drug users in the treatment of genotype 2 or 3 hepatitis C chronic infection.	Liver International. 29 (7) (pp 1051-1055), 2009. Date of Publication: 2009.
Amenson, CS	An investigation into the observed sex difference in prevalence of unipolar depression. [References].	Journal of Abnormal Psychology. Vol.90(1), Feb 1981, pp. 1-13.
Amin	Lithium every second day: Is the prophylactic effect preserved?	Progress in Neuro-Psychopharmacology & Biological
Amore M	Long-term treatment of geropsychiatric depressed patients with venlafaxine.	Journal of Affective Disorders. 46(3):293-6, 1997 Dec.
Amsterdam JD	Selegiline transdermal system in the prevention of relapse of major depressive disorder: a 52-week, double-blind, placebo-substitution, parallel-group clinical trial.	Journal of Clinical Psychopharmacology. 26(6):579-86, 2006
Amsterdam, JD	Sustained efficacy of gepirone-IR in major depressive disorder: a double-blind placebo substitution trial. [References].	Journal of Psychiatric Research. Vol.38(3), May-Jun 2004, pp. 259-
Ananthakrishnan A.N	Sleep disturbance and risk of active disease in patients with crohn's disease and ulcerative colitis.	Clinical Gastroenterology & Hepatology. 11(8), 965-971, 2013.
Anderson IM	The effect of acute citalopram on face emotion processing in remitted depression: a pharmaco MRI study.	European Neuropsychopharmacology. 21(1):140-8, 2011 Jan.
Andrade C.	Continuation and maintenance ECT: A review of recent research.	Journal of ECT. 18 (3) (pp 149-158), 2002. Date of Publication: 2002.
Andrade, C	Mania as a side effect of electroconvulsive therapy.	Convulsive Therapy. Vol.4(1), 1988, pp. 81-83.

Andreescu, C	Effect of comorbid anxiety on treatment response and relapse risk in late-life depression: Controlled study.	The British Journal of Psychiatry. Vol.190(4), Apr 2007, pp. 344-349.
Andreescu, C	Late-life depression: Evidence-based treatment and promising new directions for research and clinical practice.	Psychiatric Clinics of North America.Vol.34(2),335-355.2011
Andrews, G	Reducing the burden of depression.	The Canadian Journal of Psychiatry Vol.53(7), Jul 2008, pp. 420-427.
Andrews, G	Using epidemiological data to model efficiency in reducing the burden of depression.	Journal of Mental Health Policy and Economics. 3(4),175-186. 2000
Angst J	The depressive spectrum: diagnostic classification and course.	Journal of Affective Disorders. 45(1-2):31-9; discussion 39-40, 1997
Anonymous	Agomelatine: AGO 178, AGO178, S 20098.	Drugs in R & D. 9(3):177-83, 2008.
Anonymous	Opinion and evidence in neurology and psychiatry.	CNS Drugs. 17(5): p 363-370. 2003.
Anonymous	Quetiapine. A me-too neuroleptic; no panacea.	Prescrire International. 20(121):257-61, 2011 Nov.
Anonymous	Withdrawing patients from antidepressants.	Drug & Therapeutics Bulletin. 37(7):49-52, 1999 Jul.
Ansell, E.B	The association of personality disorders with the prospective 7-year course of anxiety disorders.	Psychological Medicine. Vol.41(5), May 2011, pp. 1019-1028.
Ansseau M.	Objective: remission of depression in primary care. The Oreon Study.	European Neuropsychopharmacology. 19 (3) (pp 169-176), 2009.
Anton R.F.	What is craving? Models and implications for treatment.	Alcohol research & health : the journal of the National Institute on
Antypa N	Cognitive reactivity: investigation of a potentially treatable marker of suicide risk in depression.	Journal of Affective Disorders. 122(1-2):46-52, 2010 Apr.
Apil SR	A stepped care relapse prevention program for depression in older people: a randomized controlled trial.	International Journal of Geriatric Psychiatry. 27(6):583-91, 2012 Jun.
Appelros, P	A review on sex differences in stroke treatment and outcome.	Acta Neurologica Scandinavica. Vol 121(6), Jun 2010, pp. 359-369.
Arato M	A 1-year, double-blind, placebo-controlled trial of ziprasidone 40, 80 and 160 mg/day in chronic schizophrenia: The Ziprasidone Extended Use in Schizophrenia (ZEUS) study.	International Clinical Psychopharmacology. 17 (5) (pp 207-215), 2002
Ardern M.	How long should the elderly take antidepressants? A double-blind placebo-controlled study of continuation/ prophylaxis therapy with dothiepin.	British Journal of Psychiatry. 162 (FEB.) (pp 175-182), 1993.
Arendt M.	Withdrawal symptoms do not predict relapse among subjects treated for cannabis dependence.	American Journal on Addictions. 16 (6) (pp 461-467), 2007. Date of
Argus, Geoffrey	Perceived social problem solving, perfectionism, and mindful awareness in clinical depression: An exploratory study.	Cognitive Therapy and Research. Vol.32(6), Dec 2008, pp. 745-757.
Armitage R.	The effects of antidepressants on sleep in patients with depression.	Canadian Journal of Psychiatry. 45 (9) (pp 803-809), 2000. Date of
Arnason B.G.W.	MS forum/MS over the past 17 years.	International MS Journal. 17 (3) (pp 76-82), 2011. Date of Publication:
Aronson, Thomas A	Relapse in delusional depression: A retrospective study of the course of treatment.	Comprehensive Psychiatry. Vol.29(1), Jan-Feb 1988, pp. 12-21.
Aulitzky W.E.	Biotherapy of chronic myelogenous leukemia.	Annals of Hematology. 70 (3) (pp 113-120), 1995.
Austin MP	Use of psychotropic medications in breast-feeding women: acute and prophylactic treatment. [Review] [40 refs]	Australian & New Zealand Journal of Psychiatry. 32(6):778-84, 1998
Avery, David	Suicide, attempted suicide, and relapse rates in depression.	Archives of General Psychiatry. Vol.35(6), Jun 1978, pp. 749-753.
Ayerbe L	The natural history of depression up to 15 years after stroke: the South London Stroke Register.	Stroke. 44(4):1105-10, 2013 Apr.
Azorin J.M.	Long-term treatment of mood disorders in schizophrenia.	Acta psychiatrica Scandinavica. Supplementum. 388 (pp 20-23),
Baars M.Y.	Relapse (Number of Detoxifications) in abstinent male alcohol-dependent patients as related to personality traits and types of tolerance to frustration.	Neuropsychobiology. 67 (4) (pp 241-248), 2013.
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Appendix VI

Letters Confirming Ethical Approval

NHS

Health Research Authority

NRES Committee London - West London
Nottingham REC Centre
The Old Chapel
Royal Standard Place
NG1 6FS

Telephone: 0115 8839309

24 June 2013

Mr Joshua Buckman
Trainee Clinical Psychologist
Research Department of Clinical, Educational and Health Psychology,
UCL
1-19 Torrington Place
London
WC1E 7HB

Dear Mr Buckman

Study title:	**Relapse in depression: Can we predict who will relapse following low-intensity interventions for depression in Improving Access to Psychological Therapies (IAPT) Services?**
REC reference:	**13/LO/0684**
IRAS project ID:	**121619**

Thank you for your letter of 13th June, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

We plan to publish your research summary wording for the above study on the NRES website, together with your contact details, unless you expressly withhold permission to do so. Publication will be no earlier than three months from the date of this favourable opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to withhold permission to publish, please contact the Co-ordinator Wendy Rees, NRESCommittee.London-WestLondon@nhs.net.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see

"Conditions of the favourable opinion" below).

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Covering Letter		13 June 2013
Evidence of insurance or indemnity		
Investigator CV		
Other: CV for Professor Stephen Pilling		
Other: CV for Professor Pasco Fearon		
Other: CV for Ms Judith Leibowitz		
Other: Reply to Prof CB 22112012		22 November 2012
Other: Response from Prof Barker_Buckman review 2		17 December 2012
Other: Trainee Indemnity Letter		06 November 2009
Other: Study Flowchart	2	17 April 2013
Other: References		
Participant Consent Form	4.1	13 June 2013
Participant Information Sheet	3	13 June 2013
Protocol	2	17 April 2013
Questionnaire: Items of the Attentional Control Scale	1	17 April 2013
Questionnaire: Beck Depression Inventory	1	17 April 2013
REC application	121619/439149/1/656	26 March 2013

Referees or other scientific critique report		18 October 2012
Response to Request for Further Information		

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

Further information is available at National Research Ethics Service website > After Review

13/LO/0684 **Please quote this number on all correspondence**

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at

With the Committee's best wishes for the success of this project.

Yours sincerely

pp. D Rees

Dr Catherine Urch
Chair

Email:NRESCommittee.London-WestLondon@nhs.net

Enclosures: "After ethical review – guidance for researchers"
Copy to: *Mrs Angela Williams, Camden and Islington NHS Foundation Trust*

noclor NHS
Bedford House, 3rd Floor
125-133 Camden High Street
London, NW1 7JR

Tel: 020 3317 3045
Fax: 020 7685 5830/5788
www.noclor.nhs.uk

30 July 2013

Joshua Buckman
Trainee Psychologist
University College London
Research Department of Clinical Educational & Health Psychology
1 – 19 Torrington Place
London. WC1E 7HB

Dear Mr Buckman,

I am pleased to confirm that the following study has now received R&D approval, and you may now start your research in **the trust identified below**:

Study Title: **Relapse in depression: Can we predict who will relapse following low-intensity interventions for deressions in Improving Access to Psychological Therapies (IAPT) Services?**
R&D reference: **IRAS ID 121619**
REC reference: **13/LO/0684**

This NHS Permission is based on the REC favourable opinion given on **24 June 2013** and the most recent amendment submitted to REC on **26 June 2013**

Name of the trust	Name of current PI/LC	Date of permission issue(d)
Camden & Islington NHS Foundation Trust	**Dr Judy Leibowitz**	**30 June 2013**

If any information on this document is altered after the date of issue, this document will be deemed INVALID

Specific Conditions of Permission (if applicable)

If any information on this document is altered after the date of issue, this document will be deemed INVALID

Yours sincerely,

Mabel Saili
Senior Research Governance Officer

Cc: Sponsor Contact

noclor NHS
Bedford House, 3rd Floor
125-133 Camden High Street
London, NW1 7JR

Tel: 020 3317 3045
Fax: 020 7685 5830/5788
www.noclor.nhs.uk

May I take this opportunity to remind you that during the course of your research you will be expected to ensure the following:

- **Patient contact:** only trained or supervised researchers who hold the appropriate Trust/NHS contract (honorary or full) with each Trust are allowed contact with that Trust's patients. If any researcher on the study does not hold a contract please contact the R&D office as soon as possible.
- **Informed consent:** original signed consent forms must be kept on file. A copy of the consent form must also be placed in the patient's notes. Research projects are subject to random audit by a member of the R&D office who will ask to see all original signed consent forms.
- **Data protection:** measures must be taken to ensure that patient data is kept confidential in accordance with the Data Protection Act 1998
- **Health & safety:** all local health & safety regulations where the research is being conducted must be adhered to.
- **Serious Adverse events:** adverse events or suspected misconduct should be reported to the R&D office and the Research Ethics Committee.
- **Project update:** you will be sent a project update form at regular intervals. Please complete the form and return it to the R&D office.
- **Publications:** it is essential that you inform the R&D office about any publications which result from your research.
- **Ethics:** R&D approval is based on the conditions set out in the favourable opinion letter from the Research Ethics Committee. If during the lifetime of your research project, you wish to make a revision or amendment to your original submission, please contact both the Research Ethics Committee and R&D Office as soon as possible.
- **Monthly / Annually Progress report:** you are required to provide us and the Research Ethics Committee with a progress report and end of project report as part of the research governance guidance.
- **Recruitment data:** if your study is a portfolio study, you are required to upload the recruitment data on a monthly basis in the website: http://www.crncc.nihr.ac.uk/about_us/processes/portfolio/p_recruitment/
- **Amendments:** if your study requires an amendment, you will need to contact the Research Ethics Committee. Once they have responded, and confirmed what kind of amendment it will be defined as, please contact the R&D office and we will arrange R&D approval for the amendment.
- **Audits:** each year, noclor select 10% of the studies from each service we have approved to be audited. You will be contacted by the R&D office if your study is selected for audit. A member of the governance team will request you complete an audit monitoring form before arranging a meeting to discuss your study.

Appendix VII

Participant Information Sheet and Consent Form

Identifying the risk factors for relapse to depression after treatment

Participant Information Sheet

You are being invited to take part in a research study. Before you decide whether to take part, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and feel free to discuss it with others if you wish. If there is anything that is not clear or if you would like more information, please ask us. Your participation in this study is completely voluntary.

What is the purpose of this study?

Interventions for depression from IAPT services are very effective with the majority of people getting better. Unfortunately some people get depressed again (relapse) after they finish treatment. The reasons for relapse are not fully understood but some researchers suggest that it is related to people's cognitive control. Cognitive control is about being able to remember and use pieces of information and also being able to pay attention to certain things whilst ignoring distractions. We believe that when cognitive control is impaired it can increase the chances of having residual (left over) symptoms of depression after treatment. Having residual symptoms is one of the main risk factors to relapsing to depression. However, little research has been done on this as of yet.

We want to ask you to fill in a brief questionnaire on cognitive control on several occasions as part of this research because we believe that by recording this we can find out more about who is likely to relapse after treatment, and if this happens we want to consider how we can best help prevent relapse for people in future.

What does taking part involve?

If you agree to take part, you will be asked to sign a consent form.

As a part of your treatment in this IAPT service you will be asked to complete some very brief questionnaires with your IAPT clinician at the beginning of every treatment session. Every person that is seen in IAPT services fills in the same questionnaires each time they come for treatment. You doing this helps your IAPT clinician to look at how you are feeling week to week which helps them with planning your treatment. By everyone filling these questionnaires in it also allows NHS services to understand how effective they are at helping people with depression as a whole.

Another part of this study is for the researchers to use information from the questionnaires completed by everyone treated for depression in Camden and

Islington NHS Foundation Trust IAPT services which have been collected over the last five years. This will help the researchers understand the relationship between symptoms people have when they start treatment and any symptoms they still have when they finish treatment. This could help identify people who might get depressed again after they have finished their treatment. Information from the questionnaires you and everyone else in Camden and Islington IAPT services complete will only be able to seen by the researchers once all personal identifiers have been removed so that it is fully anonymous. This means they can't identify any individual people who have filled the questionnaires in.

For this study we would like you to complete one additional short questionnaire at the beginning of each treatment session which is about cognitive control (this takes approximately 5 minutes each time) and another questionnaire at your first and last treatment sessions (this takes about 10 minutes each time) which is about symptoms of depression. In order for us to learn more about relapse we would then like you to complete these same two questionnaires again at 3 months and 6 months after the end of your treatment with the IAPT service. It does not involve anything else on your part. You will be seen for sessions at your IAPT service just the same as you would if you weren't taking part in this research and there is nothing extra you need to do to take part.

Why have you been chosen?

We are inviting everyone starting treatment for depression between July-September 2013 in IAPT services in Camden and Islington NHS Foundation Trust to take part in this study.

What will happen to my information?

All information collected about you during the course of the study will be kept strictly confidential and stored in secure premises at UCL. Your name and contact details will be stored separately from the data collected. Both sets of information will be kept securely according to the requirements of the Data Protection Act 1998.

It is likely that the results of this study will be published, but only group results will be presented and no individual's health will be discussed. Your name will not appear on any publications or reports about this research. Your participation is strictly confidential.

Do I have to take part?

No. It is up to you to decide whether or not to take part in this study. In other words, this is voluntary. If you *do not* take part, you will still have access to your routine care in this IAPT service. If you *do* decide to take part you are still free to stop your participation at any time and have any research data withdrawn without giving a reason. If you decide to take part, you will be given this information sheet to keep and be asked to sign a consent form.

Are there any risks?

There are very minimal risks to taking part in this study. If you feel upset or concerned about filling in the questionnaires involved in this study please share your concerns with your IAPT clinician or GP, who will be able to help.

This study has received ethical approval from West London Research Ethics Committee (Ref: 13/LO/0684). All information gathered as a result of this study will be kept strictly confidential.

What are the benefits of this research?

By taking part in this study, you will contribute to a better understanding and treatment of depression with the potential to help us find ways of reducing the risk of people having residual symptoms when they finish treatment and relapsing to depression. As taking part only involves filling in questionnaires when you come to the IAPT service for your routine treatment you will not be paid to take part in this research and travel expenses are unable to be covered.

What happens when the research study stops?

Throughout the study and afterwards, your IAPT clinician or therapist will continue to treat you as s/he feels is best for you and with your agreement.

If I have any concerns

If you wish to complain, or have any concerns about any aspect of the way you have been approached or treated by members of staff due to your participation in the research, NHS or UCL complaints mechanisms are available to you. Please ask your IAPT clinician if you would like more information on this. In the unlikely event that you are harmed by taking part in this study, compensation may be available. If you suspect that the harm is the result of negligence on the part of the Sponsor (University College London) or your IAPT service, then you may be able to claim compensation. After discussing this with your IAPT clinician, please make the claim in writing to Professor Stephen Pilling who a Principal Investigator for the research and is based at University College London (using the address below). The Principal Investigator will then pass the claim to the Sponsor's insurers, via the Sponsor's office. You may have to bear the costs of the legal action initially, and you should consult a lawyer about this.

Next Steps

If you have read through this information sheet and are happy to take part, then the first thing to do is to complete the enclosed consent form and return it to your IAPT clinician or send it to our research team in the envelope provided.

Contact Details

If you need any further information to help you decide whether to take part in the study, or if there is anything you do not understand, please contact:

Joshua Buckman, MSc, Trainee Clinical Psychologist
Research Department of Clinical, Educational & Health Psychology
University College London, 1-19 Torrington Place, London WC1E 7HB
email: Joshua.buckman.11@ucl.ac.uk, phone: 020 7679 2000

Thank you for taking the time to read this information sheet.

Title of project: Identifying the risk factors for relapse to depression after treatment
Head Researcher: Joshua Buckman

Participant Consent Form

Participant ID number:

		Please initial below
1.	I confirm that I have read the information sheet dated 13.06.13 (version 3) and have been given a copy. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
2.	I understand that my participation is voluntary and I am free to withdraw at any time, without giving a reason, without my medical care or legal rights being affected.	
3.	I understand that this study uses questionnaire measures to assess my emotional wellbeing and my cognitive control.	
4.	I understand that relevant sections of any of my medical notes and data collected during the study may be looked at by responsible individuals from University College London, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in the research. I give permission for these individuals to have access to this data. I understand that such information will be treated as strictly confidential.	
5.	I agree to take part in the above study.	
6.	I am happy to be contacted for participation in a follow-up study in future.	

Name of Participant (*please print*)	Signature of Participant	Date

Name of Researcher/PWP (please print)	*Signature of Researcher/PWP*	*Date*

Appendix VIII

The Attentional Control Scale

Items of the Attentional Control Scale

Items are scored on a 4-point scale (1= almost never; 2= sometimes; 3= often; 4= always)
R = reverse-scored item

1. It's very hard for me to concentrate on a difficult task when there are noises around. (R)

2. When I need to concentrate and solve a problem, I have trouble focussing my attention. (R)

3. When I am working hard on something, I still get distracted by events around me. (R)

4. My concentration is good even if there is music in the room around me.

5. When concentrating, I can focus my attention so that I become unaware of what's going on in the room around me.

6. When I am reading or studying, I am easily distracted if there are people talking in the same room.

7. When trying to focus my attention on something, I have difficulty blocking out distracting thoughts.

8. I have a hard time concentrating when I'm excited about something. (R)

9. When concentrating I ignore feelings of hunger or thirst.

10. I can quickly switch from one task to another.

11. It takes me a while to get really involved in a new task. (R)

12. It is difficult for me to coordinate my attention between the listening and writing required when taking notes during lectures. (R)

13. I can become interested in a new topic very quickly when I need to.

14. It is easy for me to read or write while I'm also talking on the phone.

15. I have trouble carrying on two conversations at once. (R)

16. I have a hard time coming up with new ideas quickly. (R)

17. After being interrupted or distracted I can easily shift my attention back to what I was doing before.

18. When a distracting thought comes to mind, it is easy for me to shift my attention away from it.

19. It is easy for me to alternate between two different tasks.

20. It is hard for me to break from one way of thinking about something and look at it from another point of view. (R)