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Treatment of Schizophrenia in the 21st Century: Towards a more Personalised Approach

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1. Introduction

'Canst thou not minister to a mind diseased, pluck from the memory a rooted sorrow, raze out the written troubles of the brain, and with some sweet oblivious antidote cleanse the fraught bosom of that perilous stuff which weighs upon the heart?'
Macbeth, William Shakespeare

'You look at where you're going and where you are and it never makes sense, but then you look back at where you've been and a pattern seems to emerge. And if you project forward from that pattern, then sometimes you can come up with something'
Zen and the Art of Motorcycle Maintenance, Robert Pirsig

What are the prospects for advances in the treatment of schizophrenia as the 21st Century unfolds? It is clear that many advances have been made in the 100 years since Eugen Bleuler's important monograph *Dementia Praecox or the Group of Schizophrenias*, compiled detailed clinical descriptions of his asylum patients (Bleuler 1911; 1950). Bleuler is remembered for introducing the term schizophrenia, in preference to Kraepelin's dementia praecox, but his monograph is an exemplar of comprehensive psychopathological description, and as the title of the monograph suggests, Bleuler conceived that schizophrenia was a group of conditions, rather a single nosological entity.

Although advances have undoubtedly occurred, considered reflections about the seminal contributions of Bleuler - and indeed Kraepelin - in this centenary year, may make one wonder whether these treatment advances are a somewhat thin veneer, rather than the step change required. It could be argued that progress has been more due to changes in societal values and attitudes rather than the development of effective novel interventions – either pharmacological or psychological.

We are unfortunately still some way off from understanding the neuroscience of this family of disorders, and developing rational therapies built on that understanding. It is indisputable that the antipsychotic medication of today is essentially a variant of pharmacology developed through serendipitous discovery 50 years ago. Thus in the second

decade of the 21st Century, the 'Dopamine Hypothesis' is still the dominant paradigm, and a newly introduced antipsychotic (asenapine) - with dopaminergic pharmacology - is the new kid in town. Yet exciting advances in neuroscience have, and are being made, and slowly but surely we are taking small steps forward to understand the brain. But for those of us impatient to have better treatments and interventions sooner rather than later, these scientific advances, seem too small and too slow. Take molecular genetics and bioinformatics for example; these are perhaps two of the most exciting areas of biology and are beginning to have an impact on other areas of medical therapeutics such as cancer and diabetes, and provide a signpost to 'personalised medicine'. Yet recent genome wide association (GWAS) studies of large samples, have demonstrated that in schizophrenia around 1000 or more genetic variants of low penetrance may be implicated in the heritability of schizophrenia. The crux of the schizophrenia enigma is that we are dealing with a complex family of disorders affecting the most complex of cognitive functions, namely information processing. Whatever else it is, the genus schizophrenia is hugely complex but future treatments should benefit from an explosion of findings in basic and clinical neuroscience, provided they can be translated into new therapies.

The World Health Organisation (WHO) estimates that schizophrenia, depression, epilepsy, dementia, alcohol dependence and other mental, neurological and substance-use (MNS) disorders constitute 13% of the global burden of disease, surpassing both cardiovascular disease and cancer (WHO 2008). Worldwide, schizophrenia is 3rd highest ranked MNS disorder after depression (1st) and Alcohol-use disorders (2nd), considerably higher than epilepsy (7th) and Parkinson's disease (13th) (see Table 1). The amount of health lost because

Table 1. The global burden of mental, neurological and substance use (MNS) disorders*

	Worldwide		High income countries**		Low- and middle-income countries	
Rank	Cause	DALYs*** (millions)	Cause	DALYs (millions)	Cause	DALYs (millions)
1	Unipolar depressive disorders	65.5	Unipolar depressive disorders	10.0	Unipolar depressive disorders	55.5
2	Alcohol use disorders	23.7	Alzheimer's & other dementias	4.4	Alcohol use disorders	19.5
3	Schizophrenia	16.8	Alcohol use disorders	4.2	Schizophrenia	15.2
4	Bipolar affective disorder	14.4	Drug-use disorders	1.9	Bipolar affective disorder	12.9
5	Alzheimer's & other dementias	11.2	Schizophrenia	1.6	Epilepsy	7.3
6	Drug-use disorders	8.4	Bipolar affective disorder	1.5	Alzheimer's & other dementias	6.8
7	Epilepsy	7.9	Migraine	1.4	Drug-use disorders	6.5
8	Migraine	7.8	Panic disorder	0.8	Migraine	6.3
9	Panic disorder	7.0	Insomnia (primary)	0.8	Panic disorder	6.2
10	Obsessive compulsive disorder	5.1	Parkinson's disease	0.7	Obsessive compulsive disorder	4.5
11	Insomnia (primary)	3.6	Obsessive compulsive disorder	0.6	Post-traumatic stress disorder	3.0
12	Post-traumatic stress disorder	3.5	Epilepsy	0.5	Insomnia (primary)	2.9
13	Parkinson's disease	1.7	Post-traumatic stress disorder	0.5	Multiple sclerosis	1.2
14	Multiple sclerosis	1.5	Multiple sclerosis	0.3	Parkinson's disease	1.0

*Examples of MNS disorders under the purview of the Grand Challenges in Global Mental Health Initiative.
**World Bank criteria for income (2009 gross national income (GNI) per capita): low income is US $995 equivalent or less; middle income is $996-12995; high income is $12996 or more.
***A disability-adjusted life year (DALY) is a unit for measuring the amount of health lost because of a disease or injury. It is calculated as the present value of the future years of disability-free life that are lost as a result of the premature deaths or disability occurring in a particular year.

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Table 1. The global burden of mental, neurological and substance-use (MNS) disorders.

of a disease or injury can be best estimated using Disability-Adjusted Life Years (DALY) which is calculated as the present value of the future years of disability-free life that are lost as a result of the premature deaths or disability occurring in a particular year. As shown in Table 1, schizophrenia accounts for 16.8 million DALYs on a global basis, ranging from ~1.6m to ~16m for high and low income countries respectively. The economic and social consequences of mental ill health are considerable and impact differently on developed and developing countries. The drain on national wealth is highly significant;

for example the social and economic costs of mental illness in Scotland were recently calculated at 8% of GDP perhaps around £10b sterling (SAMH, 2007).

In this chapter I will review the current status of treatment for schizophrenia in terms of effectiveness and safety, and discuss what treatment advances have been made in the last century, and how treatment interventions might and should develop as the 21st century unfolds. The emphasis of the chapter will be on pharmacological treatment and the scope for new drugs, but I will also discuss briefly the place of community systems of care, the role of inpatient services, rehabilitation and recovery models, and to a much lesser degree I will also discuss the developing role of psycho-social interventions.

2. Clinical considerations

The lifetime prevalence of schizophrenia is approximately 1% (0.70 – 1.10%) and incidence rates vary from 0.2 to 0.7 (Picchioni & Murray 2007; McGrath 2006). The onset of symptoms typically occurs in early adult life (average age 25 years), and occurs earlier in men than in women (Aleman, 2003). Schizophrenia is characterised by three key symptom domains: *positive symptoms*, such as auditory hallucinations, delusions, and thought disorder; *negative symptoms*, including anhedonia, social withdrawal, affective flattening, and demotivation; and *cognitive dysfunction*, particularly in the domains of attention, working memory, and executive function (Tamminga & Holcomb 2005). Schizophrenia is typically a life-long condition characterised by acute symptom exacerbations and widely varying degrees of functional disability. About 25% of people with schizophrenia are resistant to treatment with antipsychotic medication; treatment resistance is usually defined as a lack of clinically important improvement in symptoms, usually positive symptoms, after 2 to 3 regimens of treatment with standard antipsychotic drugs for at least 6 weeks. Of those people with schizophrenia who do benefit from antipsychotic medication, an additional 30% to 40% are residually symptomatic despite adequate antipsychotic treatment (Kane et al 1988).

About three-quarters of people with schizophrenia suffer recurrent relapses and continued disability. Outcome appears to be worse in people with the following factors: 1) an insidious onset of symptoms where initial treatment is delayed; 2) social isolation; 3) a strong family history of schizophrenia or other major mental disorder; 4) people living in industrialised countries and urbanised communities; 5) men appear to fair worse than women; and 6) in those people who misuse drugs especially cannabis, and possibly from an early age under 16 years (Jablensky et al 1992). Drug treatment is generally more successful in treating positive symptoms, but up to one third of people derive little benefit, and negative symptoms are notoriously difficult to treat. Adherence to treatment plans appears to be a particular challenge in schizophrenia due to many factors but including reduced or absent insight into the nature of their mental change. About half of people with schizophrenia do not adhere to treatment in the short term and adherence is even lower in the longer term (Johnstone, 1993).

The term schizophrenia is of course rather imprecise, and is defined clinically rather than on the basis of any biopathological markers and refers to a spectrum or family of psychotic disorders, with a range of clinical phenotypes. This clinical heterogeneity will be familiar to all clinicians treating people with 'schizophrenia', but within the spectrum of schizophrenic illness the classification systems of ICD10 (WHO) and DSM4 (APA) help provide reasonable reliability about diagnosis, at least in general terms. Risk factors associated with the aetiology of schizophrenia include the following: 1) a positive family history (reflecting at least in part genetic factors); 2) obstetric complications; 3) developmental difficulties; 4) central nervous system infections or other insults in childhood; 5) cannabis use; and 6) acutely traumatic life events (McGrath, 2006). The precise contributions of these factors, and ways in which they may interact, are unclear. For example, the heritability of schizophrenia has been estimated to be as high as 81% and recent genome wide association (GWAS) studies of large sample size, demonstrate that the clinical heterogeneity of schizophrenia probably reflects, a complex biological heterogeneity (Sullivan et al 2003). GWAS studies suggest that probably ~1000 genetic variants of low penetrance (Purcell et al 2009; Shi et al 2009; Stefansson et al 2009) and other individually rare genetic variants of higher penetrance, along with epigenetic mechanisms are responsible, *pari passu* with environmental factors, such as those above, in contributing to a complex and varied clinical phenotype. The lack of understanding of the mechanisms whereby the above aetiological factors (genetic and environmental) interact to initiate the complex pathobiology of schizophrenia is the key reason for the relative lack of progress in the development of novel drug treatments. All the antipsychotic medication that is currently in use (first and second generation) is all predicated on the so-called 'Dopamine Hypothesis' (discussed below) and share a common putative mechanism of action, namely dopamine antagonism. The benefits of 'major tranquilisers' such as chlorpromazine were first observed in the 1950s by serendipity rather than from a rational understanding of the key drug targets needed to treat schizophrenia. Unfortunately fifty years later we still await a new class of antipsychotics that have a mechanism of action predicated on advances in understanding the neuroscience of the condition.

3. Pharmacotherapy

Increasing evidence suggests that serious mental illness is neurodevelopmental and the onset of pre-psychotic symptoms occurs in adolescence, at a time when the cerebral cortex is still developing. As with many complex disorders (e.g. hypertension, epilepsy, and diabetes), there appear to be many aetiological pathways that might lead to the final mixture of behavioral signs and symptoms we label 'schizophrenia'. If there is general agreement that the key symptom domains present in schizophrenia: positive, negative, cognitive and affective, are a priority for treatment, then to what extent do currently available antipsychotic drugs succeed in ameliorating such symptoms and difficulties? Another important question is how well tolerated are the available drugs and what adverse effects are associated with them? In addressing these questions it is important to understand that the evidence base of randomised controlled trials (RCTs) that we might use to address these issues has been generated almost entirely by the pharmaceutical industry for the purpose of obtaining a license to market a particular therapeutic moiety in a particular jurisdiction. Another pitfall that is worth being aware of, is a tendency to accept the results of systematic reviews uncritically. While many such reviews can be useful, they reflect the sum of their

parts; if the constituent studies are defective then misleading summary statistics may result. Furthermore such RCTs almost always, with one or two notable exceptions, provide information about efficacy rather than effectiveness in 'real world' rather than idealised, clinical settings and rarely provide information about cost benefit analysis. There are of course exceptions to this, but in general these are the exception rather than the rule. So with this important caveat in mind, what can we conclude about the efficacy of the current licensed medicinal products?

We have recently completed a thorough review of the published literature of RCT evidence for BMJ Clinical Evidence (Barry et al 2012). In preparing this review for *Clinical Evidence* of the clinical trial literature for interventions for schizophrenia, a comprehensive search strategy identified all relevant publications, and those studies meeting reasonable quality standards were then included as described. Despite such a careful triage process, that aimed to include only good quality RCTs, it is clear that many studies we included have serious failings. Moreover, and perhaps surprisingly, objective assessment of the available evidence base for the efficacy of antipsychotic medication (and other interventions) is much less convincing than one would have hoped. Common issues being: small underpowered studies, sample bias, less than transparent methodology and data analysis, inappropriate outcome measures, to name but a few. Although in many trials haloperidol has been used as the standard comparator, the clinical trial evidence for haloperidol itself is much less impressive than one might expect (Barry et al 2012). By their very nature systematic reviews and RCTs provide only *average* indices of probable *efficacy* in groups of individuals recruited to the study in question. Although many RCTs attempt to limit inclusion criteria to a single category of diagnosis from DSM4 or ICD10, many studies include individuals with different types of schizophrenic diagnosis such as schizoaffective disorder. In all RCTs, even those recruiting according to DSM-4 or ICD10 diagnoses, there will still be considerable clinical heterogeneity, as will be recognised by clinicians treating people with 'schizophrenia' or psychotic conditions.

Clearly a more *stratified* approach to clinical trials would help identify those subgroups who appear to be the best responders to a particular intervention. To date however there is little to suggest that stratification on the basis of clinical characteristics successfully helps predict which drugs work best for which patients. There is a pressing need for the development of biomarkers with clinical utility, for mental health problems. Such measures could help stratify clinical populations or provide better markers of efficacy in clinical trials, and would complement the current use of clinical outcome scales. Clinicians are also well aware that many patients treated with antipsychotic medication, develop significant and particular adverse effects such as EPS or weight gain. Again our ability to identify which patients will develop which adverse effects is poorly developed, and might be assisted by employing biomarkers to stratify patient populations. In future the use of biomarkers that can be used in the clinic to help determine diagnostic response groups will represent an important advance.

Another important consideration is that the DSM-4 which has so dominated interventional research in schizophrenia for many years may have inadvertently inhibited drug development. Although the DSM-4 includes negative symptoms, the diagnostic criteria for schizophrenia can still be met in patients with hallucinations and/or delusions alone, without the other symptoms associated with the disorder. As a result people included in

trials have constituted a rather heterogeneous clinical group. This may have resulted a bias towards the development of treatments for positive (reality distortion) symptoms and compromised the discovery of interventions for negative or cognitive symptoms: potentially another reason for the paucity of effective therapeutics. These considerations are reflected in the support for DSM-5 to include dimensions of pychopathology in addition to diagnostic class (http://www.dsm5.org). If implemented in DSM-5, there may well be a requirement for symptom domains such as depression, anxiety, thought disorder, negative and cognition to be assessed. As discussed above this could improve drug development and afford better opportunities for psychopathology to be mapped onto neural substrates as proposed in the NIMH Research Diagnostic Criteria initiative (Cuthbert & Insel 2010). These authors have discussed in detail how 'the inertia of diagnostic orthodoxy has exerted a powerful hegemony over any alternative approaches, leaving us with much debate but little data with which to construct a new nosology'.

3.1 First and second-generation antipsychotics

The results of the BMJ Clinical Evidence review tend to indicate that as far as antipsychotic medication goes, current drugs are of some, if limited, efficacy in many patients, and that most drugs cause side effects in most patients. Although this is a rather downbeat conclusion, this will not be too surprising to clinicians in the field, given their clinical experience and our knowledge of the pharmacology of the available antipsychotic medication. Currently available antipsychotic medication has the same putative mechanism of action namely, dopaminergic antagonism with varying degrees of antagonism at other receptor sites that appear to modulate the appearance of a range of adverse consequences. More efficacious antipsychotic medication awaits a better understanding of the biological pathogenesis of these conditions so that rational therapies can be developed.

First line, standard treatment of schizophrenia and related psychotic illness is with antipsychotic drugs. All members of this drug class appear to exert their antipsychotic effect through dopaminergic antagonism. The first such drugs to be introduced included chlorpromazine and haloperidol, members of the drug group now referred to as 'first generation antipsychotics' (FGA). Chlorpromazine was synthesized in December 1951 in the laboratories of Rhône-Poulenc, and became available on prescription in France in November 1952. Its effectiveness was reflected in the transformation of disturbed wards; its commercial success stimulated the development of other psychotropic drugs (Delay, Deniker & Harl, 1952). As is well known FGA can cause severe adverse effects such as extra-pyramidal side effects including Parkinsonism and acute dystonia, as well as hyperprolactinaemia and sedation. Attempts to address these adverse effects led to the development of second-generation antipsychotics (SGA). When the SGA were introduced they were commonly known as 'atypical antipsychotics' to distinguish them from the FGA; the terms FGA and SGA are to be preferred as they infer less about the nature of the compound. The systematic review for BMJ Clinical Evidence (Barry et al 2012) summarises a considerable body of evidence from many RCTs and systematic reviews. This shows that the second-generation antipsychotics, amisulpride, clozapine, olanzapine and risperidone appear to be more effective than FGA drugs at reducing positive symptoms, and may cause similar adverse effects, but are associated with additional concerns about metabolic effects such as weight

gain, impaired glucose tolerance and hyperlipidaemia. Antipsychotics such as pimozide, quetiapine, aripiprazole, sulpiride, ziprasidone and zotepine appear to be as effective as standard antipsychotic drugs in improving positive symptoms. But again, these drugs can cause adverse effects in some patients similar to other FGA and SGA drugs. It should be noted that the use of pimozide has been associated with sudden cardiac death at doses above 20 mg daily. Antipsychotic maintenance treatment reduces relapse rates from 54% to 20% within approximately 10 months (absolute risk difference (ARD) = 37%; relative risk reduction (RRR) = 66% weighted) which translates as a NNT of 3, which is considered a large effect size (Leucht et al 2011).

It is worth emphasising however that we now appear to have a range of compounds that in some patients at least, and for some time, help to control positive psychotic symptoms. While this is very important, this benefit may come with associated adverse consequences in other ways for some patients, such as cardio-metabolic side effects that can have a major impact on physical health. Clinicians therefore will need to exercise careful and skilled judgement about which antipsychotic to use in order to benefit individual patient's symptoms, and minimise adverse health effects. There is real scope for the pharmaceutical industry to develop new drugs for positive symptoms – perhaps dopaminergic antagonists – that are less toxic and prone to cause adverse health effects.

As noted above data from trials provides little help in gauging how an individual patient will respond to or suffer from any one treatment. It has become apparent in recent years that a priority area for psychiatrists must be to ensure that the physical health of patients is monitored and addressed, given that patients with schizophrenia often have significant chronic co-morbidities such as diabetes and heart disease.

There is limited evidence to indicate whether any antipsychotic other than clozapine is effective in people with treatment-resistant schizophrenia. In people resistant to standard antipsychotic drugs, clozapine may improve symptoms compared with other first-generation and second generation antipsychotic agents, but this benefit must be balanced against the likelihood of important adverse effects such as neutropaenia, cardio-metabolic effects and sedation. It is also worth stating that quoted estimates of the prevalence of treatment resistance (around 25%) are likely to be a considerable underestimate. In the Scottish Schizophrenia Outcomes Study (Hunter et al 2009), 40% of a representative sample of 1000 people attending services with ICD10 schizophrenia, were prescribed clozapine, which could be considered a proxy for treatment resistance.

3.2 Negative symptoms and cognitive impairment

While there is evidence of efficacy of antipsychotics with respect to positive symptoms, there is much less evidence of benefit of these agents on negative symptoms. Negative symptoms were first described by Kraepelin in 1919 as the 'avolitional syndrome' (Kraepelin 1919) and the term now refers to the absence or reduction in normal behaviours and functions (Mäkinen et al 2008) Negative symptoms are listed from the PANSS Negative Subscale in Table 2. Persistent negative symptoms can be either primary or secondary and usually persist during periods of clinical stability, when positive symptoms may have remitted and they often interfere with the ability to perform normal everyday functions.

Negative and cognitive symptoms are important areas where the drugs currently available have only minimal benefit and patients have considerable unmet need (Kirkpatrick 2006; NICE 2011).

N1 Blunted affect

N2 Emotional withdrawal

N3 Poor rapport

N4 Passive / apathetic social withdrawal

N5 Difficulty in abstract thinking

N6 lack of spontaneity and flow of conversation

N7 Stereotyped thinking

Table 2. Positive and Negative Symptom Scale - Negative Subscale.

A substantial number of studies now show that the severity of cognitive impairments in people with schizophrenia is predictive of getting back to meaningful activity, perhaps work, social functioning and independent living (Green 1996). Increased recognition of this is the key reason for the burgeoning interest in Neurocognition as a target for either pharmacological or psychological intervention strategies ('cognitive remediation' for example see Wykes & Spaulding 2011).

In the BMJ Clinical Evidence review (Barry et al 2012), we were unable to reach conclusions about the effect of antipsychotic drugs on cognitive symptoms due to a lack of RCTs and the lack of standardized validated measures in available trials. This is clearly an area that pharma and the research community must address. There are signs again that this is changing. The FDA has recognised the importance of cognitive impairment in schizophrenia and funded development of a clinical cognitive test battery, the MATRICS: Measurement & Treatment Research to Improve Cognition in Schizophrenia (see Buchanan et al 2005 and www.matrics.ucla.edu). The MATRICS comprises seven cognitive domains: Speed of processing, Attention/Vigilance, Working Memory, Verbal Learning & memory, Visual Learning & memory, Problem solving, and Social Cognition. The FDA has recommended that the MATRICS Consensus Cognitive Battery should be used as the standard set of cognitive tests for all clinical trials of potential cognitive enhancers in schizophrenia. This is an important initiative which, although MATRICS may well be over engineered with consequent reduced utility for many patients, has undoubtedly influenced the use of cognition as an outcome measure in clinical trials, and perhaps helped encourage the development of pharmacological cognitive enhancers. The FDA has endorsed both cognitive impairment (Buchanan et al 2005) and negative symptoms (Kirkpatrick et al 2006) as distinct therapeutic targets or domains and this approach has attracted support (e.g. Harvey et al 2006). There is however an alternative view that there is overlap between the constructs, 'negative symptoms' and 'cognitive impairment' in schizophrenia (Laughren & Levin, 2011).

It is recognised that both these domains may be largely, though not exclusively, residual phase phenomena. This has been a relatively neglected phase of the condition when patients' positive symptoms are to some extent attenuated or at least manageable, and the individual would aspire to improve the quality of their lives, but is hampered in this, by residual negative symptoms and cognitive impairments. For these reasons the FDA have now recommended that in all future clinical trials targeting either primary negative symptoms or targeting cognitive impairments, researchers should collect data on both these domains (Laughren & Levin, 2011).

We have shown that negative symptoms as assessed by PANSS are strongly related to psychosocial functioning as assessed by a number of different scales across eleven different European centres (Hunter et al 2011). Given the nature of such negative symptoms and their frequent occurrence in schizophrenia, it is reasonable to assume that negative symptoms are an important causal contribution to reduced psychosocial functioning in schizophrenia. This has important implications for the care of people with schizophrenia. Firstly, given that successful community care will require good or at least, adequate psychosocial functioning, improving negative symptomatology is an essential prerequisite. Secondly, physicians, psychologists, researchers and the pharmaceutical industry need to refocus on this area in order to develop effective treatments. There is some evidence that this is starting to occur (see www.ClinicalTrials.gov) although hampered by a still largely incomplete understanding of the pathogenesis and neurobiology of schizophrenia. There are several novel drugs in development – some Phase 3 Trials – that appear to work by modulating glutamatergic function, that may help negative and neurocognitive symptoms.

4. New drugs for schizophrenia?

The 'dopamine hypothesis of schizophrenia' proposes that excessive subcortical dopamine release, linked to prefrontal cortical dopaminergic dysfunction is central to the pathogenesis of schizophrenia (Van Rossum, 1966). Although all antipsychotics modulate dopamine activity in the brain, via dopaminergic antagonism, there is no incontrovertible evidence that schizophrenia is the result of a primary dopamine abnormality. Dopamine dysregulation is likely to be a 'downstream' or a secondary consequence of the primary biological causes of the condition (Coyle, 2006). Despite these qualifications, the dopamine antagonists have provided considerable benefit to many patients in reducing positive symptoms and there are no licensed antipsychotics as yet which do not have dopaminergic antagonism as a key part of their pharmacological profile. It is clear however that the biological basis of schizophrenia is likely to be complex and much more than a dysregulation of dopamine metabolism. As already mentioned GWAS studies sign post several different areas of cellular metabolism that appear involved in pathogenesis and help identify new candidate genes as putative drug targets. For example, the gene *KCNH2* was identified in a large meta-analysis of five independent data sets to be associated with schizophrenia. The *KCNH2* gene encodes a membrane-spanning potassium channel and the expression of *KCNH2-3.1* is specifically increased within the hippocampal formation of individuals with schizophrenia and in normal individuals who carry risk-associated alleles (Huffaker et al, 2009). Genetic linkage and association studies have also implicated members of the Neuregulin-ErbB receptor (NRG-ErbB) signalling pathway as risk factors for

schizophrenia **(**Buonanno et al, 2010). These examples are cited simply to illustrate how genetic studies can help identify genes or groups of genes associated with schizophrenia, and how by understanding the functional significance of such genes we may discover new drug targets.

There is increasing interest in a 'glutamate hypothesis' of schizophrenia that postulates a disruption of excitatory neural pathways through N-methyl-D-aspartate (NMDA) (glutamate) receptor hypofunction (Coyle, 2006; Krystal et al 1994). Evidence for the role of glutamate in schizophrenia comes from many different sources. For example glutamate antagonists can cause psychotic symptoms, suggesting that schizophrenia may involve glutamate dysfunction (Kantrowitz & Javitt 2010; Coyle 2006). For example 'angel dust' or Phencyclidine (PCP), an N-methyl-D-aspartate (NMDA) antagonist, has been taken as a recreational drug particularly in the USA, and can cause positive psychotic symptoms in humans ('PCP Psychosis' has been reported). Pharmacological models employing NMDA receptor blockade by phencyclidine (PCP) and MK-801 (Cochran et al. 2003; Rujescu et al. 2006) induce changes in animal brains that have been considered to resemble those occurring in schizophrenia such as cognitive difficulties (e.g. reduced set shift ability) or reduced brain activity in prefrontal cortex (so called hypofrontality). There are also reports of altered levels of glutamate signaling pathway metabolites in cerebrospinal fluid and in post-mortem brain (Coyle, Tsai et al. 2003). Candidate genes relating to Glutamate metabolism e.g. *NRG1*, *ERBB4* and *DTNBP1* have also been found to associate with schizophrenia in some studies (Buonanno 2010). As a result of these studies and other evidence there is considerable interest in drugs that may modulate glutamatergic function in patients. Several major studies are underway including trials of LY2140023, an mGlu2/3 receptor agonist (Weinberger, 2007; Kinon et al. 2011).

Dopamine and glutamate both interact at a cortical level where glutamatergic and dopaminergic cells modulate each other: glutamatergic pyramidal cells in hippocampus and PFC are modulated by dopamine and dopaminergic firing is modulated by glutamate (see Figure 1). Perhaps in designing what individual patients require from medication, we could envisage combining different drugs needed to improve different sorts of psychopathology. For example drugs that act to improve NMDA function may improve negative, but not positive symptoms and dopaminergic antagonism may well be required to treat positive symptoms. One possible future treatment development might involve patients receiving different drug combinations to target different types of symptom domains: affective, positive, negative and cognitive (see Figure 2). In this paradigm, drugs for negative or cognitive impairment are used adjunctively with antipsychotics; indeed a number of potential cognitive enhancers are in early clinical trials at present in this way. In many ways this type of approach parallels that used in other chronic disease areas such as cancer or cardiology, where advances have been made using combinations of agents. In this way, polypharmacy could be a rational strategy, rather than viewed negatively as at present.

The search for new drugs in psychiatry will be greatly facilitated when biomarkers are available that allow patient subgroups to be identified for treatment stratification in RCTs. Biomarkers that have utility in the clinic such as genetics or EEG methods, rather than sophisticated imaging techniques such as MRI that are poorly tolerated by paranoid or anxious patients will be required. These methods used in combination with translational drug discovery paradigms rather than conventional linear drug discovery approaches (viz.

Phase 1 - 3 clinical trials) will be important drivers for drug discovery. This new approach to drug discovery combined with the search for new drug targets using the emerging understanding of the biology of schizophrenia, and the use of different drugs in combination to target different symptom domains, are likely to produce much more effective treatments in future for the schizophrenias, than those currently available.

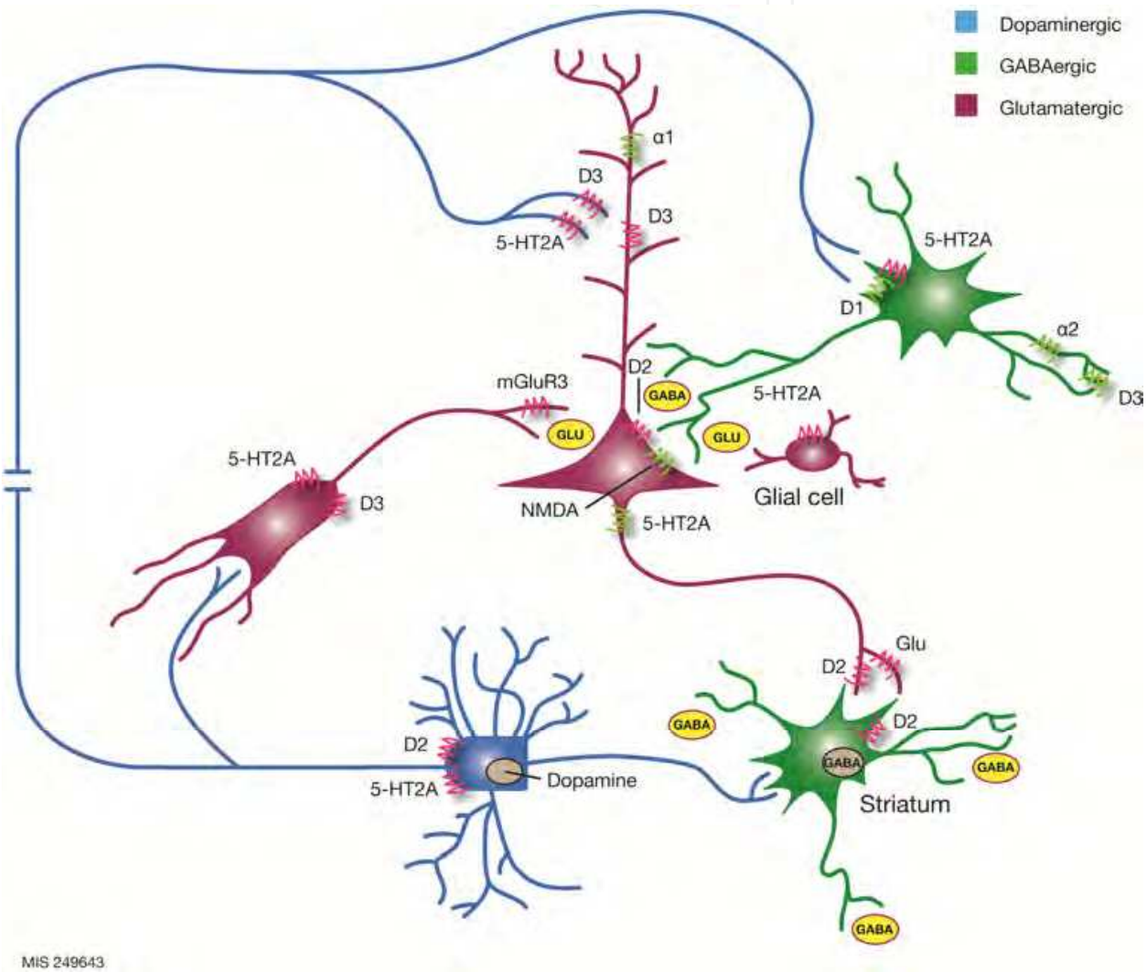

Fig. 1. Modulation of pyramidal glutamatergic neurones by GABAergic and Dopaminergic neurones. (adapted with thanks, from Nature Reviews Drug Discovery)

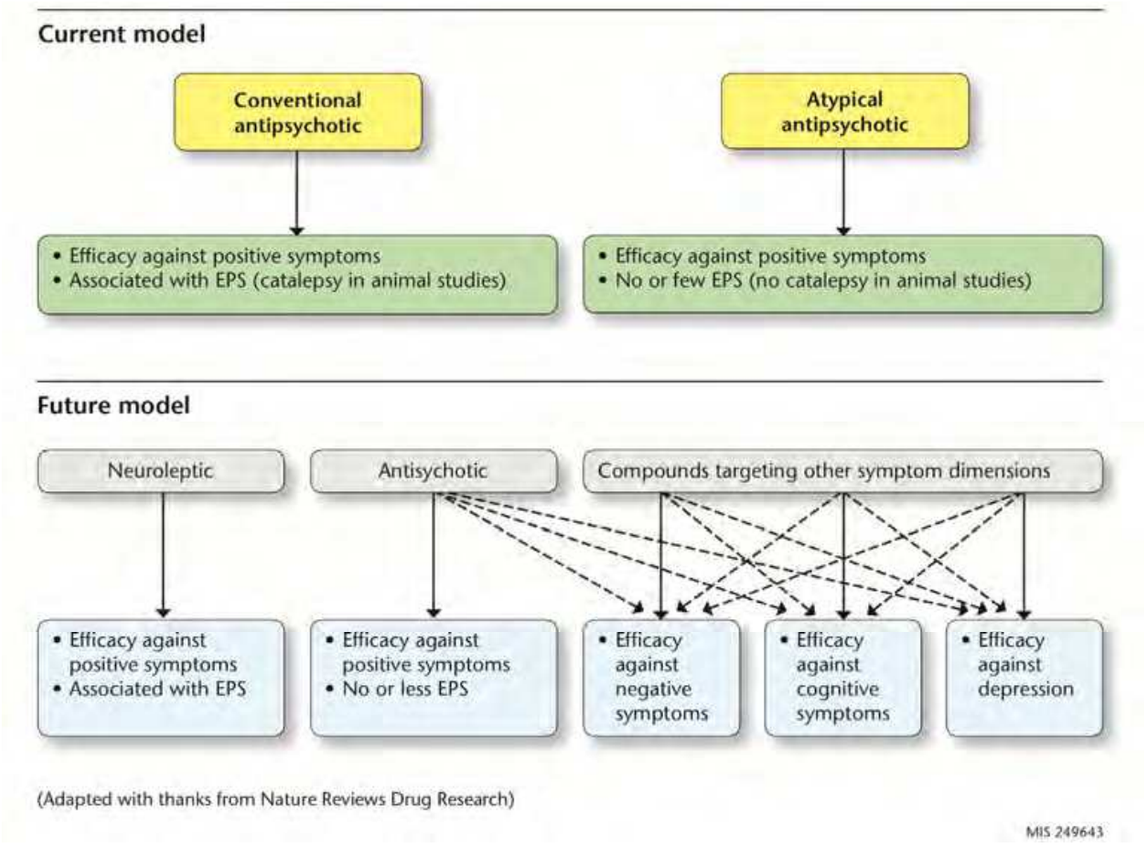

Fig. 2. Targeting symptom domains in schizophrenia: The case for rational polypharmacy.

5. Community-based care for schizophrenia

A huge change has occurred in the last few years in the way people with schizophrenia are looked after in more developed societies. Up until around the 1980s most people with serious mental health conditions were looked after in large mental hospitals (or 'institutions') many built in the Victorian era. My own hospital, Gartnavel Royal in Glasgow, dates from 1804, gaining its 'Royal' charter in 1824, and moving from the city centre to the current green field site in 1843. In the 1950s the number of resident patients peaked at over 900, almost twice the number of patients that the hospital had originally been built to accommodate. Up until the advent of what became known as 'community care', such large asylums were common throughout the UK and other countries, and existed as care communities with their own rules and mores, medical and nursing superintendents, 'therapy' of various sorts was provided such as farm work, chapels for worship, and at Gartnavel, even a golf course! Until the 1990s Glasgow, a medium sized post-industrial city, had 6 large asylums surrounding the city to accommodate people with chronic mental illness, many of whom suffered from schizophrenia. Today, with a new hospital building opened in 2008, Gartnavel Royal has only around 150 beds. Moreover most of the other asylums in Glasgow have closed completely and most patients with schizophrenia now live in the wider community. This brief example of the rise and decline of the mental hospital from Glasgow is representative of a general pattern of change that has occurred across Europe and the USA in the last two decades. While there is no doubt that one of the drivers for this change was an increased realisation of the harmful effects

of institutionalisation, it is also true that financial considerations were perhaps the paramount motivation for the downsizing of mental facilities, and indeed their privatisation.

One of the countries in the vanguard of this change was Italy, where in 1978, the introduction of the Basaglia Law started a revolution in psychiatric care that concluded with the closure of the Italian state mental hospital system in 1998 (Tansella 1986). This process of reform known as *Psichiatria Democratica,* allowed for the introduction of community care and the closure of the old asylums, and was passed through the Italian Parliament with little difficulty given support across the political spectrum. Thus Italy was the first country to start a process of deinstitutionalization of mental health care and develop a community-based psychiatric system. In the UK and USA, similar developments gathered pace in the 1980s, under the leadership of Margaret Thatcher and Ronald Reagan respectively. During these changes effective and innovative service models emerged for supporting patients out with hospital and the phased closure of the psychiatric hospitals required a comprehensive, integrated community mental health service to develop. The objective of community care was an attempt to reverse the long-accepted practice of segregating the mental ill in large institutions; whether attempts to promote integration in the community have always been successful is open to question, and there is concern that many patients are now living an isolated, disconnected life in the 'community' with little regular support from psychiatric and other staff.

Most patients with schizophrenia now live in accommodation within the 'community' as demonstrated in the Scottish Schizophrenia Outcomes Study (SSOS, Hunter et al 2009). Undoubtedly there is less asylum based institutionalisation, but SSOS also demonstrated concerns about the poor quality of life and increased social isolation of the many people with schizophrenia, and the challenges for staff in supporting people in diverse settings, with pervasive positive and negative symptoms, poor psychosocial functioning, poor physical health, and vulnerability to exploitation by others. There has also been concern about the drift of many people with schizophrenia back into institutionalisation in prisons or to a life of homelessness. Individuals with comorbid personality disorders, forensic history and /or substance misuse are also a concern, and require complex, integrated models of care from motivated staff. These difficulties have been highlighted by small numbers of high profile cases where violence or homicide has occurred, sometimes due to a failure of community care supports. One well known example was the Christopher Clunis case in England (Coid, 1994), but similar failures of care have occurred in all countries.

Despite the development of community based services for people with schizophrenia and other psychotic illnesses, in-patient facilities in the UK are under considerable pressure with high rates of bed occupancy. Concern has recently been expressed by a number of groups such the Royal College of Psychiatrists in the UK and patient advocacy organisations about conditions in some in-patient facilities, which have been found to be counter therapeutic. Clearly good quality in-patient and residential facilities are essential with clear integrated care pathways and support from acute psychiatric care and rehabilitation facilities. Availability of suitable accommodation, integrated into the healthcare system, where people with schizophrenia can be supported on a regular basis and tailored to meet their needs is essential. In the UK and many other countries much of this accommodation lies within the private sector; with services sometimes having difficulty accessing patients who have failed to adhere to treatment as they become more paranoid and disorganised in their behaviour. It seems clear that while some people with schizophrenia will be able to live in their accommodation with less support, many will need a higher level of support from care

workers, psychiatric nurses, and psychiatrists. Sometimes referred to as 'supported accommodation', facilities managed by a non-statutory provider such as a mental health charity, are often able to encourage socialisation, provide support, allow monitoring of mental state and behaviour, and encourage rehabilitation after the individual has left hospital. Such residential settings with mental health support workers usually have good links to local GPs, psychiatrists and the community mental health team (CMHT). Clearly in a condition where many sufferers lack insight into having mental illness, staff in the community, whether from the CMHT, primary care or mental health support workers, will all have a role to play to improve adherence to treatment plans. Twenty years ago within the asylum, the care plan for patients and the necessary communication between staff responsible for a patient's welfare appears relatively straightforward. Compare this with today's community based network of care that may involve psychiatrist and CMHT, especially the community psychiatric nurse (CPN), GP and primary care team, pharmacist, support workers from possibly several non-statutory mental health support organisations, housing associations, social work, advocacy and the legal profession. Add to this the involvement of more specialist health teams for addictions and early onset intervention, in-patient facilities at the local psychiatric unit, and as patients get older the need to involve physical health specialists and you have a highly complex network of individuals from different agencies, who need to communicate effectively and coordinate the delivery of the care plan: no mean task! Staff will increasingly need to use databases, IT networks and smart phones to meet these challenges. Schizophrenia is a long term condition, yet comprehensive long term support for the challenges patients face such as anxiety, depression, reality distortion, negative symptoms and cognitive impairments, is often less well-resourced than newer more fashionable services. For example in recent years early intervention services have been developed (Marshall & Rathbone 2011; NICE 2011), often ahead of the production of evidence of superior effectiveness for such services. In contrast the provision of adequate resources in order to develop lifelong services for people with schizophrenia that aspire to do more than treat the initial presentation, acute relapses and maintain the status quo, should be our goal.

5.1 Importance of physical healthcare

It has been estimated that people with schizophrenia have a 20% shorter life expectancy than the general population (Newman & Bland 1991), and increased vulnerability to diabetes type 2, coronary artery disease, hypertension, and emphysema. One hypothesis for such vulnerability is that the lifestyles of people with serious mental illnesses, is often associated with poor diet, obesity, lack of exercise, high rates of smoking, and use of alcohol and street drugs. Antipsychotic medication is also associated with added health risks from causally related weight gain, hyperglycaemia and the onset of diabetes, hyperlipidaemia, and abnormal findings on ECGs and cardiotoxicity. Antipsychotics have also been associated with other side effects that may affect health, including prolactin elevation, cataract formation, movement disorders, and sexual dysfunction. The significant health risks associated with schizophrenia and the medications used in its treatment, emphasise the importance of physical health monitoring in this patient population. Yet even when recognised there is evidence that patients with serious mental illness are less likely to receive standard levels of care for most diseases (De Hert et al 2011). A key priority needs to be to consider how services can be re organised to deliver better and more timely care for people with schizophrenia; while this is a challenge for inpatient care (Miller, 2011), it is an

even greater challenge in relation to the majority of patients living in community settings. Solutions may vary from region to region, but will need to take account of lifestyle and local cultural factors, medication side effects, and the reluctance of, and barriers to, people with psychotic conditions contacting and using general medical services. Importantly we should also not forget the Inverse Care Law (Tudor Hart, 1971). Working as a general medical practitioner in South Wales, Tudor Hart recognised that 'the availability of good medical care tends to vary inversely with the need for it in the population served. This inverse care law operates more completely where medical care is most exposed to market forces, and less so where such exposure is reduced'. Although not written specifically about those with mental illness in mind, it would however, seem to apply no less, and given the current economic pressures in many countries for so called efficiency savings in the cost of healthcare through the use of liberalised markets, those with severe mental illness may find themselves at even greater disadvantage than at present. An important next step in the management of physical health in this population will be to improve awareness and training in those doctors, including psychiatrists, who already care for the mentally ill, and to encourage them to follow guidelines for standardizing investigations, assessments and care given to mental health patients. Recommendations include taking regular measurements of patients' weight and BMI, monitoring blood pressure, checking glucose levels and carefully evaluating their medication history. Smoking is more prevalent in people with schizophrenia than comparisons with the general population, but encouragingly there has been some success in the use of specialist services for smoking cessation help.

5.2 Psychosocial interventions

It is beyond the scope of this chapter to review in detail the increasing trend to employ psychosocial adjunctive methods in the treatment plan for people with schizophrenia. Lack of insight and poor adherence to treatment often present formidable challenges to those involved in care, as well as blocking roads to recovery. NICE (2011) has recommended that family intervention should be offered to all individuals diagnosed with schizophrenia that are in close contact with, or live with, family members and should be considered a priority where there are persistent symptoms or a high risk of relapse. Family intervention should include communication skills, problem solving and psycho-education. Psycho-educational approaches have been developed to increase patients' knowledge about, and insight into, their illness and treatment. A recent Cochrane review (Xia et al 2011) compared the efficacy of psycho-education added to standard care with that of standard care alone, and the meta-analysis showed a significant reduction of relapse or readmission rates. As the authors admit however there is a scarcity of good quality studies of adequate power, and difficulties in combining studies with different definitions of what is meant by psycho-education. A recent review of the evidence for psycho-educational interventions to improve adherence to antipsychotic medication, behavioural interventions, or compliance therapy, concluded that the jury is still out due to due to a paucity of good quality evidence (Barry et al 2012).

Although Cognitive Behavioural Therapy (CBT) was first reported as a possible therapy for people with schizophrenia in 1952, it was not recommended as a routine treatment until 2009. Research on positive symptoms has led to the hypothesis that there are specific cognitive biases affecting reasoning, attribution style and impaired self-worth (e.g. see Garety and Freeman, 1999). This led to the development of models and interventions for positive symptoms based on Cognitive Behavioural Therapy (e.g. Kuipers et al 2006 and Moritz &

Woodward, 2007). Over the last few years modified CBT for psychosis (or CBTp) has been developed. This is described as a structured and collaborative therapeutic approach, which purports to be a discrete psychological intervention. CBTp aims to make explicit connections between thinking, emotions, physiology and behaviour with respect to current or past problems. CBTp also seeks to achieve systemic change through the re-evaluation of perceptions, beliefs or reasoning hypothesised to cause and maintain psychiatric symptoms and psychological problems. The aim of CBTp seems overly ambitious for most patients, but may help for the individual make sense of their psychotic experiences, and reduce the associated distress and impact on functioning. Targeted outcomes, though not always achieved, include symptom reduction (positive or negative symptoms and general symptoms including mood), relapse reduction, enhancement of social functioning, development of insight, amelioration of distress, and the promotion of recovery. Although there is support for CBTp and in England it is recommended by NICE (2011), other evidence is more equivocal such as the Cochrane Review in 2011 which concludes that Trial-based evidence suggests no clear and convincing advantage for cognitive behavioural therapy over other and sometimes much less sophisticated therapies for people with schizophrenia (Jones et al 2011).

The effectiveness of available interventions for negative symptoms is far from satisfactory: Cognitive-behavioral therapy (CBTp) shows some impact on negative symptoms but the effect sizes are small (Wykes et al 2008). Even psychosocial approaches specifically developed to reduce negative symptoms have failed to produce convincing effects.

6. Rehabilitation, recovery and recovery-based services

Perhaps surprisingly, the advent of the asylums in the late 18th century was associated with therapeutic optimism, as 'moral treatment' for the mentally unwell was advocated. Such treatment emphasized an optimistic approach, physical activity, minimal coercion and comfortable, healthy environments for people with serious mental health problems and recovery was defined as the abatement of symptoms (Tuke, 1813). However by the beginning of the 20th century, the asylums were overcrowded, a situation which lasted well into the 1990s and the early optimism gave way to different approaches which emphasised containment, loss of more personalised approaches and the classification of mental disorders by Kraepelin and Bleuler tended to stress the chronic and often progressive course in people diagnosed with schizophrenia. Throughout the last 50 years the use of neuroleptic medication - the major tranquilisers, soon rebranded as 'antipsychotics' - has been recognised to help the abatement of positive symptoms. However in the late 20th century, a different notion of what recovery might mean, re-entered the mental health arena that had echoes back to the optimism of the early asylum era. The developments in psychiatric rehabilitation and deinstitutionalisation, as well the developing service user/survivor

movement gave the term recovery new meanings in the late 1980s and the 1990s. Unlike the traditional clinical understanding of recovery, focussing on the abatement of symptoms, this new use of 'recovery' did not necessarily equate with abatement of symptoms but instead emphasised a renewed sense of self and encouragement for a return to a more self-directed meaningful life (Mental Health Commission of New Zealand, 2011). This distinction between clinical recovery and personal recovery has not always been well understood by mental health practitioners although there is increasing evidence that practitioners are now increasingly using the principles of recovery in their work (Lieberman et al 2008; Davidson et al 2006).

Lieberman attempted a synthesis between the different perspectives, arguing that clinical neuroscience (psychiatric practice) and the newer meanings of recovery, as defined by the advocacy movement were complementary and not mutually exclusive or competing (Lieberman et al 2008). However it should be recognised that some proponents of the 'recovery movement', view most mainstream psychiatric services as emphasising an approach where 'the assessment of personal deficits' is an important element. This would include rehabilitation services, which while apparently more optimistic and 'recovery-focused', share with acute mental health services the same philosophy namely that treatment should follow assessment of 'deficits' (symptoms, issues, impairments etc.). The service user/survivor movement on the other hand, is based on the notion of self-determination and developing personal strengths and has been influenced by social models of disability which assert that it is society that disables, not the impairments of individuals (Oliver, 1990). Consequently some of the recovery literature coming out of the user/survivor movement may be more likely to question the basic tenets of the mental health system such as the concept of mental illness itself, or the need for compulsory treatment, or the process of assessing individuals' needs or difficulties. Unfortunately there is sometimes an impression that some proponents of the recovery movement are not only challenging, but antagonistic towards the views and expertise of mental health professionals who are sometimes caricatured as being stuck in a traditional mind set, cataloguing deficits and beholden to medicalised models of mental health (Slade, 2009). In is not an overstatement to say that developing interventions and strategies to improve mental health will clearly benefit from all interested parties sharing ideas, learning from one another and working together in respectful manner. Interestingly survivor literature on recovery often tends to focus on the deficits external to the individual with the diagnosis, for example in support services or housing in wider society, more than in the individual themselves. In the author's experience rehabilitation team professionals often echo similar views in their frustration to help people find meaning in their lives: at Gartnavel Royal Hospital the legacy of Dr RD Laing is never far from one's mind.

Encouragingly there does appear to be a developing shared understanding of the importance of personal recovery within rehabilitation, and other mental health professionals. One simple yet powerful technique promoted in recovery is supporting an individual to make sense of what has happened in their life; such life stories can not only help someone add meaning to their life, and move forward, but may also help professionals and carers to understand their journey (Scotti 2009). The Scottish Recovery Network (SRN) (http://www.scottishrecovery.net) has promoted this idea in its Narrative Research Project which has provided support for people to tell their stories. In Table 3, the Key Themes of Recovery from the SRN are described in more detail including: recovery as a journey; hope, optimism and strengths; more than recovery from illness; control, choice, and inclusion; self-management; finding meaning and purpose; relationships.

Recovery as a journey

The recovery journey can have ups and downs and some people describe being *in recovery* rather than recovered to reflect this.

Hope, optimism and strengths

Hope is widely acknowledged as key to recovery. There can be no change without the belief that a better life is both possible and attainable. One way to realise a more hopeful approach is to find ways to focus on strengths.

More than recovery from illness

Some people describe being in recovery while still experiencing symptoms. For some it is about recovering a life and *identity* beyond the experience of mental ill health.

Control, choice and inclusion

Taking control can be hard but many people describe how it important it is to find a way to take an active and responsible role in their own recovery. Control is supported by the inclusion of people with experience of mental health issues in their communities. It is reduced by the experience of *exclusion*, *stigma* and *discrimination*.

Self-management

One way to gain more control over recovery is to develop and use self-management techniques. One such self-management tool which Scottish Recovery Network promotes is the Wellness Recovery Action Plan.

Finding meaning and purpose

We all find meaning in very different ways. Some people may find spirituality important, while others may find meaning through employment or the development of stronger interpersonal or community links. Many people describe the importance of feeling valued and of *contributing* as active members of a community.

Relationships

Supportive relationships based on belief, trust and shared humanity help promote recovery.

Table 3. Key Themes of Recovery*
*Reprinted with thanks from the Scottish Recovery Network:
http://www.scottishrecovery.net/

While recovery is a unique and individual experience it is possible to identify key themes and ideas in relation to the experience. The above list, while not exhaustive, highlights some of the most commonly identified elements.

Psychiatric rehabilitation had its origins in the programme of asylum closures in the 1980s and 90s with the aim of helping community integration and promotion of independence of individuals with mental health problems. But where then does psychiatric rehabilitation stand today, following deinstitutionalisation and the influence of the recovery movement? Today the focus of much of the work within many rehabilitation services in the UK is with individuals who have not progressed within acute admission wards and are unable to be discharged, because of a complex interplay of factors between the individual and their environment. Often rehabilitation teams, comprising psychiatrists, social workers, nurses, psychologists and occupational therapists and other mental health professionals, work to reduce functional impairments and the intensity of symptoms using a variety of approaches, combining pharmacological treatment, independent living and social skills training, psychological support to individuals and their families, housing, and access to meaningful activities. The ethos of the rehabilitation team is to work collaboratively in order to empower people to find their way forward and live a meaningful life. Clearly the recovery movement has influenced, and continues to influence the development of rehabilitation (and other) services, some of which are now being rebranded as 'supported recovery

services'. The Scottish Recovery Network has produced a web-based tool (Scottish Recovery Indicator, SRI) that has been designed to help mental health services facilitate change in practice and promote a more recovery orientated service. Some NHS services in Scotland are using to the SRI tool to help service providers assess the extent to which their services are 'recovery focussed'. Most such initiatives are management, rather than professionally, driven, but do usefully highlight issues in relation to inclusion, rights, equalities and diversity. Personal recovery approaches have become central to mental health policy in many English-speaking countries. A comparative analysis of policy direction in seven countries (New Zealand, Australia, Canada, England, Scotland, USA and Italy) notes a good deal of convergence in their priorities. It is instructive to list these priorities as they give an important outline of the shape of services in many modern psychiatric care systems and also emphasise how influential the recovery movement has been. The following themes occur throughout the seven services: promotion of wellbeing and anti-discrimination; improving access and enhancing range of services; ensuring an adequate, competent and skilled workforce; focusing on service user participation, responsiveness and recovery; integrating / linking health and social sectors; promoting evidence-based, measurable and accountable responses; wellbeing promotion and prevention; early intervention and anti-discrimination; 'holistic' responses for people with mental illness including talking therapies, drug therapies, peer support, recovery education, support in crisis, support in housing, support in education and employment, and advocacy (Compagni, Adams & Daniels, 2006).

7. Future directions

As we consider the centenary of Bleuler's influential monograph and the introduction of the term 'schizophrenia', it is timely to ask how much progress has been made in understanding the pathogenesis of schizophrenia and the development of effective treatments. As will be clear from this chapter, despite the considerable advances in neuroscience, there is still some way to go in understanding the neuroscience of schizophrenia. We still have much to learn about what changes in brain structure and function occur and why. Despite the advances in genetics in the last few years, what we know is that schizophrenia probably involves multiple genetic markers - perhaps more than 1000 genes - involved in establishing and maintaining a complex network of molecular relationships within the brain. We still have much to understand about gene interactions, gene expression and how environmental effects, such as psycho-social stressors and trauma, may affect gene expression and cell function. We are also beginning to appreciate that psycho-social factors may also impact on brain structure and function via genetic and non-genetic mechanisms, particularly at vulnerable times in development, but how this occurs is poorly understood despite interesting work in animal models. It seems clear however, that only from an understanding of the biology of pathogenesis will more coherent and better treatments eventually emerge. It is very concerning recently that a number of major pharmaceutical companies have decided to move out of CNS research, and in particular schizophrenia research, due to the scale of current challenges, including the lack of good drug targets, and lack of effective techniques and methods for diagnosing and/or stratifying patient populations, and monitoring response. There is an urgent need to make progress on the development of biomarkers that have utility in ordinary clinical settings: MRI or SPECT/PET scanning will be useful research tools in specialised settings but none of these imaging methods will support the sort of biomarkers we require: low cost, easily accessible, and available in clinics

that patients are comfortable about visiting. Genetic and EEG methods look the most promising in this regards with data being sent electronically to expert centres for fast reporting back to clinicians. This sort of telemedicine approach is likely to develop first in memory clinics for the assessment of Alzheimer's disease, but will probably then move to schizophrenia, if biomarkers are available.

These advances are likely to be some way off but there are approaches we could introduce now to begin to develop a more personalized medicine approach in schizophrenia. We have discussed above that schizophrenia needs to be seen as a long term condition and a more integrated care pathway developed that recognises this. Many guidelines for schizophrenia appear to be little more than a list of short term interventions advocated on the basis of a less than adequate evidence base, where conflicts of interest of authors are seldom transparent. In my view guidelines need to utilize the framework of the patient's timeline, and in this way the challenges of middle and late stage illness may receive the attention they merit. It is still quite puzzling and unhelpful that most psychiatrists do not use any sytematic set of standardized assessments. Symptoms and functionality are reported in narrative, subjective form, without the use of any form of adjunctive standardised assessment. It is diificult to understand why this has occurred, given the absence of any biomarkers in psychiatry. In my view mental health specialists, but particularly psychiatrists need to agree on a menu of measures in order to standardise the assessment of positive, negative, cognitive and psycho-social functioning in schizophrenia. While Bleuler is to be praised for his detailed clinical descriptions, the quality of which appear absent from many case notes today, 100 years later we should be moving to a system of more standardized assessment in order to augment narrative descriptions using available reliable and valid instruments. These measures could usefully help clinicians assess, in a more individulaised way, which areas of need are a priority for individual patients, and would facillitate better mapping of progress and assessment of outcome. Although such methods have been embraced by psychologists and even nurses within mental health, and by physicians in other specialties (e.g. Apgar Scores by paediatriacians: Casey et al 2001; Glasgow Coma Scale by neurologists: Matis & Birbilis 2008), psychiatrists, at least in most of the UK, but probably more widely, seem uniquely resistant to this development. Gilbody et al (2002) reported a survey of the use of outcome measures in psychiatric practice in the UK involving 500 consultant psychiatrists practising in the NHS and reported that only 6.5% of clinicians treating patients with schizophrenia routinely used standardised measures to assess clinical changes over time. At a recent focus group on this issue (personal communication), this resistance was still evident; some of the views noted included: 'standardized measures are appropriate for research but not clinical practice'; 'divides a continuously fluctuating process into arbitrary categories'; 'assessments have poor psychometric properties: validity, reliability and sensitivity to change'; 'detracts from therapeutic relationship'. It is interesting that DSM-5 may well embrace this type of dimensional approach within broad diagnostic categories. Such an approach could begin to help develop and tailor pharmacological and psychological interventions for individual patients. For example, packages of care could be planned to meet an individual's needs for control of positive, affective or negative symptoms, and cognitive impairments. Personalised medicine though is not just about assessments and tailoring interventions, it is also about listening to patients (and their carers) and working with them to promote clinical and personal recovery.

There is no doubt that the social and institutional reforms in many developed countries, with emphasis on human rights, dignity, and attempts (as yet not too successful) to reduce stigma have been important steps forward. The change from institutionalised care in large isolated asylums, to community based care using smaller scale modern facilities, has been important. While I have discussed the limitations of antipsychotic medication, there is no doubt that the availability of such medication has made an important contribution to the management of acute episodes and prevention of relapse. The philosophical approach of personal recovery is becoming better accepted by mental health professionals and has been incorporated into the care offered to many patients by many services. As we understand better the biology of schizophrenia, rational opportunities to develop more effective and less toxic treatments will follow. However it is likely that more effective psychological interventions such as cognitive remediation (McGurk et al 2007; Wykes & Spaulding 2011) will also become important and we will be clearer about what constitutes the key elements of successful talking treatments. It is interesting that such therapies appear to be evolving from quite a narrow CBT focus to talking therapies that involve a broader scope that embraces the principles of personal recovery.

So what's next for schizophrenia as the century unfolds? The brain is by far the most complex organ and organisation in the known world. Comparisons with computers or the internet are rather facile, and probably unhelpful. Our understanding of neuroscience and specifically of the brain will continue to progress given adequate human and economic resources, although current reductionist approaches may have limitations in understanding the complexity involved. It is likely that advances from other scientific disciplines such as physics, mathematics, genetics and molecular biology will help to provide new insights into how psychiatric disturbance is caused and maintained. Such insights may help identify new potential treatments; however it is likely that knowledge from areas as yet not envisioned or conceptualised may provide a paradigm shift in our thinking about psychiatric illness and schizophrenia that hopefully will herald much more progress in the 21st century, than the modest progress we have seen in the last since Bleuler.

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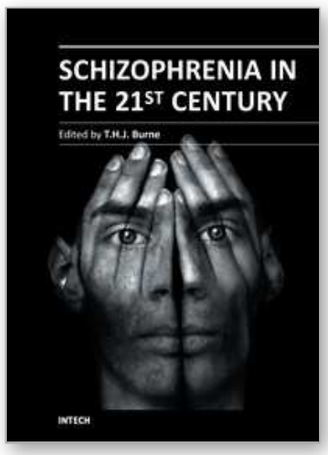

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Schizophrenia is a poorly understood but very disabling group of brain disorders. While hallucinations and delusions (positive symptoms of schizophrenia) feature prominently in diagnostic criteria, impairments of memory and attentional processing (cognitive symptoms of schizophrenia) are attracting increasing interest in modern neuropsychiatry. Schizophrenia in the 21st Century brings together recent findings on this group of devastating disorders. We are still a long way from having effective treatment options, particularly for cognitive symptoms, and lack effective interventions and ways to prevent this disease. This volume covers various current options for therapy, clinical research into cognitive symptoms of schizophrenia and preclinical research in animal models.

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