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Clinical response to SSRIs relative to cognitive behavioral therapy in depression: a symptom-specific approach

Both antidepressant medication and cognitive behavioral therapy (CBT) have been found efficacious in reducing overall depression severity[1,2]. A patient-level meta-analysis[3] showed that medication was slightly more efficacious than CBT and that this was independent of pre-treatment depression severity. A crucial step in improving clinical practice would be to identify factors that do play a role in the clinical response to treatment and, thus, can be used in decision support tools guiding the personalization of treatment[4].

In a previous paper published in this journal[5], we reported that individual symptoms differ in their response to antidepressant medication relative to CBT. In general, medication was more efficacious than CBT in reducing affective symptoms (i.e., depressed mood and psychic anxiety) and cognitive symptoms (e.g., feelings of guilt and suicidal thoughts), whereas their efficacy was comparable for most symptoms related to, for example, sleep, arousal and bodily functions. We also applied network estimation techniques to reveal the complex patterns in which changes in individual symptoms were related and could, consequently, detect those symptoms that were directly affected by medication (i.e., direct treatment effects) or only indirectly affected through impact on other symptoms (i.e., indirect treatment effects).

As the neurobiological actions and consequent clinical profiles of antidepressant classes differ, it is important to study one medication class at the time. While we previously had lumped together data regarding different classes of antidepressants[5], the current analysis focused on only one group, selective serotonin reuptake inhibitors (SSRIs), as these are the most commonly prescribed antidepressant drugs. From our previous sample[3,5], we hence selected patients with a DSM-based primary diagnosis of a depressive disorder (major depressive disorder or dysthymia) participating in trials comparing an SSRI with CBT. The 599 patients (68.4% women; mean age: 42.7 years) of six trials with complete pre- and post-treatment symptom data comprised the sample of the current study. Of these patients, 391 (65.3%) received an SSRI and 208 (34.7%) CBT.

Statistical software R (version 4.0.5) was used to estimate a network including treatment condition (SSRI relative to CBT) and changes in individual depressive symptoms during treatment. As this combines a binary variable (treatment condition) with continuous variables (change scores), the network was estimated with package *mgm*[6] using a mixed graphical model and visualized with package *qgraph*[7].

Changes in individual depression symptoms were assessed using the 17 separate items of the Hamilton Depression Rating Scale (HDRS)[8], both before and after treatment (8-16 weeks after the pre-treatment assessment). To improve the interpretation, we divided the 17 symptoms into five categories: two affective symptoms (i.e., depressed mood and psychic anxiety), four cognitive symptoms (i.e., feelings of guilt, suicidal thoughts, loss of interest in work/activities, and retardation – including concentration difficulties), seven arousal/somatic symptoms (i.e., agitation, somatic anxiety, general somatic symptoms – including lack of energy, genital symptoms, hypochondriasis, and gastrointestinal symptoms), three related to sleep (i.e., early night, middle night, and early morning insomnia), and one concerning lack of disease insight. Items were scored from either 0 to 4 (all affective and cognitive symptoms, arousal/somatic symptoms of anxiety, and hypochondriasis) or 0 to 2 (most arousal/somatic symptoms, all sleep symptoms, and lack of insight).

In the resulting network, the only direct beneficial effects of SSRIs relative to CBT were found for the two affective symptoms, i.e., depressed mood and psychic anxiety (both connection strengths = –.05). Changes in depressed mood were mainly related to changes in psychic anxiety (connection strength = .17), all four cognitive symptoms (connection strengths ranging from .08 for feelings of guilt to .24 for loss of interest in work and activities) and, although less strongly, specific arousal/somatic symptoms (e.g., connection strengths of .11 for gastrointestinal problems and .08 for general somatic symptoms including lack of energy). Changes in psychic anxiety were mainly related to changes in depressed mood (connection strength = .17) and most arousal/somatic symptoms (e.g., connection strengths of .20 for somatic anxiety and .08 for agitation).

Interestingly, we also found two detrimental effects of SSRIs relative to CBT, both on arousal-related symptoms, i.e., somatic anxiety (connection strength = .09) and agitation (connection strength = .03). Changes in somatic anxiety were related to changes in specific other symptoms (connection strength of .20 for psychic anxiety), whereas changes in agitation were not or only very weakly related to changes in other symptoms.

Our findings show that, relative to CBT, SSRIs are more efficacious in improving depressed mood and psychic anxiety, whereas they are less efficacious in improving somatic anxiety and agitation. This suggests that patients suffering more from the former two symptoms and less from the latter two may benefit the most from SSRIs, and vice versa.

To explore this, we distinguished groups of patients (quartiles, Q1 to Q4) based on a pre-treatment severity measure in which these four symptoms were summed and weighted by their connection strengths as derived from the network. As expected, the overall efficacy of SSRIs over CBT increased in groups scoring higher on this severity indicator (i.e., Cohen's d=.10 in Q1, .01 in Q2, –.05 in Q3, and –.16 in Q4).

In conclusion, our study is the first distinguishing the direct and indirect symptom-specific effects of SSRIs relative to CBT (and vice versa) and can, consequently, provide important insights into the potential mechanisms of clinical change during

the different treatments. SSRIs mainly have direct beneficial effects on the two affective symptoms, which is in line with an individual patient meta-analysis comparing SSRIs to a placebo control condition[9]. The most important indirect effects of SSRIs are found for all cognitive symptoms, including highly clinically relevant symptoms such as suicidal thoughts and loss of interest, and specific arousal/somatic symptoms. SSRIs have detrimental effects on two specific arousal symptoms (i.e., somatic anxiety and agitation), which are common side effects of SSRIs that can be captured by the HDRS.

We also found that information from these networks could help in improving the identification of patients who were the most likely to benefit from one treatment relative to the other. That is, patients who suffered more from depressed mood and psychic anxiety and less from somatic anxiety and agitation were the most likely to benefit from SSRIs, whereas the opposite was true for CBT. It is, however, important to note that effect sizes were small (Cohen's d ranging from .10 in Q1 to –.16 in Q4), somewhat limiting the relevance of findings for clinical practice.

A symptom-specific approach is valuable, but also challenging, as more research is needed on the reliability and validity of assessing individual symptoms with individual (HDRS) items. In addition, the current categorization of symptoms – just like any categorization – may be overly simplistic, as, for example, affective symptoms may also comprise a cognitive component and cognitive symptoms an affective component. However, we do want to emphasize that a symptom-specific approach is highly promising in capturing the complex clinical response to depression treatments and in guiding the personalization of treatments.

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COVID-19 vaccination uptake in people with severe mental illness: a UK-based cohort study

The COVID-19 pandemic has exacerbated pre-existing health inequalities between people with severe mental illness (SMI) and the general population. These inequalities are rightly regarded as a human rights issue[1]. Rapidly accumulating evidence indicates that people with SMI are disproportionately affected by COVID-19 infection, showing increased risks of hospitalization and mortality[2].

Attention has recently turned to equitable COVID-19 vaccine allocation. Drawing on ethical frameworks, there have been calls – the first one appearing in this journal[3] – to prioritize people with SMI for vaccination. Having been severely affected by the pandemic, the UK has been among the fastest countries worldwide to deploy its vaccination plan and one of the few countries to explicitly prioritize persons with SMI[4]. Evidence on vaccine uptake among population subgroups in the UK is emerging[5]. However, more fine-grained evidence of uptake among people with different psychiatric diagnoses is necessary to evaluate delivery of vaccination plans and inform mental health practitioners.

We are investigating COVID-19 outcomes using de-identified electronic health record data from the Greater Manchester Care Record (GMCR), a shared care record for 2.8 million people, comprising real-time information from primary care, hospital admissions and mental health records. Using the GMCR, we compared vaccination rates in a sample of 1,152,831 adults with and without SMI. Individuals were followed up until June 30, 2021, ahead of the UK's relaxation of COVID-19 restrictions on July 19, 2021. Approval was granted by GMCR's secondary uses and research governance process.

All patients who were registered with a general practitioner in Greater Manchester on January 31, 2020, aged 18 years or over, and with a lifetime diagnosis of SMI recorded in their primary care record, were eligible for inclusion in the SMI sample. This sample was divided into three hierarchically defined, mutually exclusive groups of individuals with schizophrenia or related psychotic disorders (N=46,859), bipolar disorder (N=3,461), and recurrent major depressive disorder (N=134,661). Alongside this, we also obtained a 10% sample of individuals with diagnoses of other depressive disorders, excluding all previously mentioned diagnoses (N=45,586). For comparison purposes, we obtained records for 922,264 age and gender-matched controls with no evidence of SMI or depressive disorders, sampled at a 4:1 ratio