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Research report

Characteristics and differences in treatment outcome of inpatients with chronic vs. episodic major depressive disorders

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ABSTRACT

Background: Approximately 20–30% of patients with Major depressive disorder (MDD) develop a chronic course of their disease. Chronic depression is associated with increased health care utilisation, hospitalisation and a higher disease burden. We identified clinical correlates and differences in treatment response of chronic MDD (cMDD) patients compared with non-chronic episodic depression in a huge sample of depressive inpatients.

Methods: Data were collected from 412 inpatients who had been diagnosed with a major depressive episode (MDE; according to ICD-10) and scored 15 or higher on the 21-item Hamilton Depression Rating Scale (HRSD-21). All subjects were participants in the German Algorithm Project, phase 3 (GAP3). Patients who were diagnosed with a MDE within the last two years or longer (herein referred to as CD) were compared with non-chronic depressive patients (herein referred to as non-CD). CD and non-CD patients were assessed for the following: psychosocial characteristics, symptom reduction from hospital admission to discharge, symptom severity at discharge, remission and response rates, and pharmacological treatment during inpatient treatment. The primary outcome measure was the HRSD-21.

Results: 13.6% ($n=56$) of patients met the criteria for chronic depression. Compared with non-CD patients, patients with CD showed increased axis I comorbidities (74% vs. 52%, χ^2 (1)=7.31, $p=.02$), a higher level of depressive symptoms at baseline and discharge, increased duration of inpatient treatment (64.8 vs. 53.3 days; $t=2.86$, $p=.03$) and lower response (HRSD: 60.0% vs. 72.0%; χ^2 (1)=3.61, $p<.04$; BDI: 40.5% vs. 54.2%; χ^2 (1)=3.56, $p=.04$) and remission rates (BDI 17.9.% vs. 29.7%; χ^2 (1)=3.42, $p=.05$. However, both groups achieved a comparable symptom reduction during inpatient treatment. The prescribed pharmacological strategy had no significant influence on treatment outcome in patients with CD.

Conclusion: Inpatients with CD show higher symptom severity, lower response and remission rates and a longer duration of inpatient treatment, although they achieve comparable symptom reduction during treatment. These findings support the need to recognise CD and its defining characteristics as a distinct subclass of depression.

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1. Background

Major depressive disorder (MDD) with a lifetime prevalence of 15% is one of the most prevalent mental disorders and can lead to severe reductions in quality of life, disability and excess mortality (Kessler et al., 2005). According to Kessler et al. (2003) and Lopez et al. (2006) in 2020 depression will rank third in overall health care costs. Approximately 20–30% of patients with a major depressive episode (MDE) develop chronic disease (Gilmer et al., 2005; Murphy and Byrne, 2012) with a medium disease duration of ~20 years (Spijker et al., 2002). According to DSM-5, chronic forms of depression are categorised as persistent depressive disorder (American Psychiatric Association, 2013) and are regarded as a distinct subtype of depression. The concept and definition of chronic depression (CD) however is different from treatment resistant depression. Due to this recent classification of CD as a distinct depressive subtype there is a corresponding growing interest in investigating the unique characteristics, risk factors and psychotherapy treatments of CD. In a recent meta-analysis the following risk factors for CD were identified: younger age of onset, longer duration of depressive episode, family history of mood disorders, psychiatric comorbidities (i.e. anxiety disorders, personality disorders and substance abuse) low level of social integration and lower severity of depressive symptoms (Hölzel et al., 2011). In over 70% of cases, chronic forms of depression begin early in life and are often associated with early childhood trauma (Hölzel et al., 2011; Wiersma et al., 2009). Patients suffering from cMDD are reported to have a more severe disease course, as evidenced by an increased suicide risk (Spijker et al., 2010), comorbidity with other psychiatric Axis I and II disorders, and increased disability in physical and psychosocial functioning (Blanco et al., 2010; Sung et al., 2013). Compared with non-chronic forms of depression, CD is associated with increased health care utilisation, hospitalisation, higher disease burden, lower response rates (Trivedi et al., 2006) and higher impact on individuals' social functioning (Gilmer et al., 2005). However, there is inconsistency between studies in regards to response rates between chronic and episodic MDD, with only certain studies reporting a difference (Sung et al., 2013). In the CO-MED trial, chronicity of illness did not differentially impact acute or long-term outcomes with selective serotonin reuptake inhibitor (SSRI) monotherapy or combination antidepressant medication treatment in patients with MDD (Sung et al., 2012). The CO-MED study reported that participants with cMDD were of greater socioeconomic disadvantage and had greater medical and psychiatric disease burden. Interestingly, the chronic and non-chronic groups did not differ in rates of remission at 12 weeks or at 28 weeks after treatment (Sung et al., 2012).

Under-treatment and social impairment are the most striking characteristics of chronic depressive disorders (Satyanarayana et al., 2009). Efficacy and effectiveness of antidepressants have been demonstrated; however several studies have reported lower response and remission rates for CD patients than for non-CD patients and higher rates of treatment-resistance (Cuijpers et al., 2010). Among the antidepressants found to be superior to placebo in treatment of CD were desipramine, fluoxetine, mocobemide, imipramine and sertraline (Bauer et al., 2002). Further proof of efficacy was confirmed for escitalopram (Hellerstein et al., 2010) and duloxetine (Hellerstein et al., 2012). Meta-analysis of the treatment of dysthymic patients demonstrated that SSRIs and TCAs are both effective, but highlighted the differential tolerance of the two drug groups (Silva de Lima and Hotopf, 2003). A recent meta-analysis found that SSRIs and TCAs do not differ in terms of efficacy, but SSRIs tend to be superior in terms of tolerance (von Wolff et al., 2013). There is evidence that patients with chronic depression particularly benefit from a combination of pharmacotherapy and psychotherapy: in a controlled randomized trial of 681 CD outpatients cognitive behavioural analysis system of psychotherapy (CBASP) was found to be as effective as pharmacotherapy (33% remission, 48% response) and most effective in combination with an antidepressant (48% remission, 73% response) (Keller et al., 2000). Kocsis et al. (2009) were unable to replicate these findings, however it should be noted that there are several limitations to this study such as the short duration of psychotherapy, with an average of 12.9 sessions per patient. Therefore, it is uncertain whether combination therapy does in fact result in higher remission and response rates (von Wolff et al., 2012).

In summary, findings regarding differences in the clinical characteristics and response patterns of CD and non-CD patients remain inconclusive. Given the recent inclusion of the CD classification within DSM-5, there currently is a deficit of relevant clinical trials. To address these issues we performed a retrospective analysis of CD patients within the German Algorithm Project, phase 3 (GAP3). GAP3 was the third and final phase of the multiphase German Algorithm Project (Adli et al., 2002; Bauer et al., 2009). GAP3 evaluated algorithm-guided treatment of inpatients with MDD compared to treatment as usual (TAU) (Adli et al., 2006). GAP3 was part of the German Research Network on Depression funded by the German Federal Ministry of Education and Research. The objective of the presented post-hoc analysis of the GAP3 database was to determine the prevalence of CD in the GAP3 sample, to define its clinical correlates and to compare treatment response to that of non-chronic episodic depression. Furthermore, we examined whether the prescribed pharmacological strategy (SSRI, SNRI, TCA, mirtazapine or lithium-augmentation) influenced treatment outcome in CD. We hypothesise that patients with CD have an increased frequency of axis I and II comorbidities, higher depressive symptom scores and lower response and remission rates compared with non-CD patients.

2. Method

2.1. Study overview

Study subjects were drawn from GAP3, a randomized controlled multi-centre trial to compare two different treatment algorithms (standardized stepwise drug treatment regimen, SSTR, and a computerised decision and expert system, CDES) with TAU. Within SSTR, three different “second-step strategies” (lithium augmentation, high dose antidepressant monotherapy, and change of antidepressant) were compared in patients nonresponsive to four-week antidepressant monotherapy during inpatient treatment. For SSTR-treated patients, physicians selected one of four possible antidepressants (sertraline, an SSRI; venlafaxine, an SNRI; reboxetine, a norepinephrine reuptake inhibitor; amitriptyline, a TCA) CDES linked individual patient response data to a probability matrix. Depending on the patient's probability of responding to the current treatment, CDES proposed either continuing or altering the current strategy, without providing explicit recommendations. Lorazepam and non-benzodiazepine hypnotics (zopiclone and zolpidem) were permitted for all patients to manage agitation, anxiety, or sleeping problems. The GAP3 study was conducted between 2000 and 2005 in six academic and four non-academic hospitals throughout Germany. The results from this study have been published in multiple research articles (Adli et al., 2006; Bauer et al., 2009; Ricken et al., 2011).

2.2. Participants

Adult inpatients (aged 18–70 years) with a primary diagnosis of single or recurrent depressive episodes (mild, moderate, or severe with or without psychotic symptoms) according to ICD-10 were eligible for the study. An additional inclusion criterion was a score of 15 or higher on the 21-item Hamilton Depression Rating Scale