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Invited review article

# Inappropriate prescriptions of antidepressant drugs in patients with subthreshold to mild depression: Time for the evidence to become practice

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ABSTRACT

Recent studies indicate that antidepressant drugs are largely ineffective in patients with subthreshold to mild depression when compared to placebo. In spite of this evidence, researchers continue to judge the prescription of antidepressant drugs to patients with subthreshold to mild depression as an adequate treatment, which in turn serves to further reinforce the undifferentiated treatment strategy adopted by clinicians. The present narrative review critically reflects on current research practice and highlights the need for a more differentiated, evidence-based clinical and research practice.



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In a recent article, Cameron and colleagues (2011) compared patients with subthreshold depression (HADS-D<8), who were diagnosed by their general practitioners (GPs) as either depressed or not depressed. They highlighted that those diagnosed as being depressed more frequently had a history of depression or anxiety and more often had received antidepressant medication (39% vs. 7%). Moreover, patients with newly initiated antidepressant medication treatment often have had an increased severity of anxiety. Based on these findings they concluded that GPs' diagnoses and subsequent treatment of depressive disorder in patients with subthreshold symptoms were appropriate.

While Cameron et al. (2011) made the case for GPs' diagnoses of depression being not as inappropriate as previously contended (Mitchell et al., 2011), their conclusions fall short on two counts: Firstly, while many of the patients diagnosed as being depressed might have been mentally distressed, GPs tended to misclassify anxious patients as being depressed. Secondly, and most importantly, antidepressant drugs are not an appropriate first-line treatment for patients with subthreshold to mild depression and thus should not be interpreted as such by researchers. The present narrative review critically reflects on this scientific practice of justifying antidepressant drug prescriptions for patients with subthreshold to mild depression

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and highlights the need for a more differentiated, evidence-based clinical *and* research practice.

The number of operationalizations of subthreshold depression varies widely (Baumeister and Morar, 2008). Most studies operationalized subthreshold depression either dimensionally, using cut-off scores of validated questionnaires and rating scales for depression or categorically, according to the DSM-III-R or DSM-IV criteria of minor depression (Baumeister and Morar, 2008). Mild depression usually refers to patients fulfilling the DSM-IV criteria of major depression with only low symptom severity or functional impairment (Kessler, 2003; NICE, 2009). The present review focuses on DSM-IV minor depression and DSM-IV major depression with subthreshold to mild symptom severity (following named subthreshold to mild depression). A subthreshold to mild symptom severity is defined as a Hamilton Rating Scale for Depression (HAM-D) score of 8–18 (NICE, 2009). In this context, it is important to mention that what the American Psychiatric Association (APA) named *mild* (HAM-D score of 8–13), *moderate* (14–18), *severe* (19–22) and *very severe* depression ($\geq 23$) was downgraded by NICE to *subthreshold*, *mild*, *moderate* and *severe* depression (Kriston and von Wolff, 2011).

Subthreshold to mild depression has been frequently shown to be associated with a deteriorated quality of life, increased mortality as compared to non-depressed and the risk of transition to more severe depression (Cuijpers and Smit, 2002; Fogel et al., 2006; Lyness et al., 2006; Nierenberg et al., 2010), underlining the need for effective interventions for patients with subthreshold to mild depression. Antidepressant drugs have become a standard treatment for these patients.

However, after a decade of great enthusiasm about the efficacy of antidepressant drugs, the last 5 years were characterized by dismantling the view of antidepressant drugs as an omnipotent medication. The current evidence highlights that antidepressant drugs are largely ineffective in patients with subthreshold and mild depression when compared to placebo (Barbui et al., 2011; Fournier et al., 2010; Kirsch et al., 2008). The frequently reported superior efficacy of antidepressant drugs to placebo (Arroll et al., 2009; Baumeister et al., submitted; Rayner et al., 2010; Schueler et al., 2011) only remained true for severely depressed patients, when data of unpublished trials were taken into account (Fournier et al., 2010; Kirsch et al., 2008; Pigott et al., 2010; Turner et al., 2008). Given the importance and unpopularity of these findings, methodological limitations of the aforementioned systematic reviews have been extensively discussed (Fountoulakis and Moller, 2011; Mathew and Charney, 2009; Nierenberg et al., 2011; Pies, 2010). Despite the given methodological limitations, however, the evidence is strong enough to refute recommendations of antidepressant drugs as a first-line treatment for patients with subthreshold to mild depression (NICE, 2009; Nierenberg et al., 2011; Pies, 2010). Consequently, the National Institute for Health and Clinical Excellence (NICE) guideline concludes that antidepressant drugs should not routinely be used to treat (persistent) subthreshold depressive symptoms or mild depression because of the poor risk–benefit ratio (NICE, 2009).

Against the background of these findings it seems time for this evidence to be reflected in both clinical and research practice. Scientific papers such as the aforementioned article by Cameron et al. (2011), however, reinforce clinicians in maintaining their undifferentiated practice of prescribing antidepressant drugs in spite of an only subthreshold to mild depression severity. In 2007, 2.9% of the US population received outpatient treatment for depression (Marcus and Olfson, 2010). Of these patients, 75% were treated with antidepressant drugs, at an annual medication expenditure of $6.6 billion (Marcus and Olfson, 2010). Based on data from the National Comorbidity Survey Replication (NCS-R) 1.6% of the US general population with subthreshold to mild major depression received treatment (APA severity classification used by Kessler et al. adapted to NICE classification) (Kessler et al., 2003), which would—based on the aforementioned rate of antidepressant drug prescriptions—result in a rate of about 1.2% of the general US population receiving antidepressant drugs despite a symptom severity of their major depression within the subthreshold to mild range. Accounting for persons with minor depression, who received antidepressant drugs, would further increase this prevalence rate.

Not all such treatments are necessarily inadequate. NICE, for example, recommend considering antidepressant drug prescription in patients with subthreshold to mild symptom severity where there is a case of "a past history of moderate or severe depression, an initial presentation of persistent subthreshold depressive symptoms that have been present for a long period (typically at least 2 years) or subthreshold depressive symptoms or mild depression that persist(s) after other interventions" (NICE, 2009, p. 471). Moreover, the prescription of antidepressant drugs might be adequate in the case of comorbid conditions such as anxiety disorders or pain conditions for which antidepressant drugs have been shown to be effective (Baumeister and Härter, 2011; Brunton et al., 2011; NICE, 2011) as well as for relapse prevention in patients who have benefited from taking an antidepressant drug (NICE, 2009). In contrast, primary prevention of new onset depression is not regarded as an area of indication for antidepressant drugs as long as not embedded in a stepped-care approach (Baldwin, 2010; Munoz et al., 2010; Reynolds et al., 2007; van't Veer-Tazelaar et al., 2009). Stepped-care approaches and (computerized) psychological interventions are favored, owing to the poor risk–benefit ratio and the low cost-effectiveness of antidepressant drug prevention as well as the circumstance that for many patients, taking an antidepressant drug to prevent the onset of depression, might be hardly conceivable (Baldwin, 2010; Munoz et al., 2010; Reynolds et al., 2007). The importance of focusing on the risk–benefit ratio of antidepressant drug interventions is once more highlighted by the study of Wu et al. (2011), who showed that antidepressant drug use is associated with an increased risk of stroke. As yet, post-stroke prevention of depression has been a major target for antidepressant drug trials with limited effect on the prevention of depression (Baldwin, 2010; Hackett et al., 2008). Thus, it seems questionable to continue the use of antidepressant drugs as a preventive measure in stroke patients, particularly as psychotherapies showed a small but significant effect on improving mood and preventing depression in this patient group (Hackett et al., 2008).

The results of Cameron et al.'s study underline that GPs substantially misclassify patients with a subthreshold depression symptom severity as being depressed and subsequently prescribe antidepressant drugs where active