HISTORICAL DOCUMENT

CPA Position Statement

Prescribing Antidepressants for Depression in 2005: Recent Concerns and Recommendations

An addendum to the Canadian Psychiatric Association
Clinical Practice Guidelines for Treatment of Depressive Disorders[1]

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Background

Clinical Practice Guidelines for the Treatment of Depressive Disorders, published in 2001 by the Canadian Psychiatric Assocation (CPA) and the Canadian Network for Mood and Anxiety Treatments (CANMAT), recommended selective serotonin reuptake inhibitors (SSRIs), selective serotonin and noradrenaline reuptake inhibitors (SNRIs), and other novel antidepressants as first-line treatments for major depressive disorder (MDD) across different age groups (1). The recommendations were based on these agents' better tolerability and safety profile, compared with tricyclic antidepressants (TCAs) and monoamine oxidase inhibitor (MAOI) agents. For adults, there was Level 1 evidence (that is, metaanalyses or replicated randomized controlled trials [RCTs]) to support these recommendations. In children and adolescents, only Level 2 evidence (that is, at least one RCT) was available to support fluoxetine and paroxetine as first-line treatments; in contrast, TCAs were "not recommended" on the basis of Level 1 evidence.

Recently, the safety of SSRIs, SNRIs, and other novel agents has been questioned in regard to their potential to cause or exacerbate aggression and suicidality (defined in this statement as emergence and [or] worsening of suicidal thoughts, behaviours, and attempts). Initially,

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reports dealt with adult patients (2,3), but subsequently, the controversy has focused mainly on children and adolescents, attracting the attention of both media and regulatory authorities (4,5).

This is a major health issue, given the increasing prevalence of depression in children and adolescents and the documented failure of TCAs to perform effectively in this population. While several published studies showed that SSRIs have significant benefit in children and adolescents, the situation was confounded when it emerged that many other industry-sponsored trials failing to find significant benefit were unpublished (6). Further, these studies included evidence of significant adverse events, such as lability, impulsivity, agitation, suicidal ideation, and self-harm behaviours. Several editorials questioned whether these unpublished negative trials were being deliberately or otherwise concealed or ignored (7).

The public and media concern about suicidality associated with SSRIs and newer antidepressants in part spurred regulatory authorities in Canada, the US, the UK, and elsewhere to mandate changes in product labelling and (or) monographs for these medications (8–10). Physicians and other health practitioners have received many notices with conflicting information from various agencies and sources. For example, some reports incorrectly reported the UK statements as a "ban" against antidepressants in children (11). Both practitioners and the public have become increasingly confused and demoralized about the state of clinical use of these medications.

The purpose of this statement is to update the CPA–CANMAT depression guidelines by reviewing the evidence base in regard to suicidality associated with antidepressants in different age groups and to provide recommendations to physicians about the clinical use of these medications. Although antidepressants are used for several disorders and conditions, this statement focuses on studies of antidepressants in MDD. The procedure followed was similar to that for the original guidelines, including the same ratings for level of evidence (1). In brief, we conducted a literature search focusing on systematic reviews and RCTs published since 2001. We also scrutinized recent reports from the major government agencies, including the reanalysis of clinical trial data from the US Food and Drug Administration (FDA) that included all known unpublished studies. From these data, we summarize the benefits and risks for prescribing antidepressants in different age groups; clinical recommendations follow. The statement was peer-reviewed by executive members of CANMAT and other external experts in the field (see Acknowledgements).

Clinical Issues in Evaluating Suicidality

Before reviewing the relation between antidepressants and suicidality, it is essential to recognize that patients of all ages who suffer from MDD and other major mental disorders are inherently at risk of suicide. Also, antidepressants are usually prescribed to people when their symptom severity (including suicidality) is highest; thus teasing out links between antidepressants and suicide is very difficult (12). Suicidality that emerges after starting an antidepressant may be due to: 1) natural worsening of the underlying depression and lack of benefit from the medication, 2) improvement in some symptoms (such as energy) before improvement in mood, 3) an unanticipated environmental trigger (for example, breakup of a relationship), 4) a specific adverse event associated with the antidepressant, or 5) a nonspecific adverse event (for example, increased anxiety or agitation) associated with the antidepressant.

Although the newer antidepressants have recently been the focus of attention, some of these concerns predate the SSRI era. For example, emergent or exacerbated suicidal ideation was described during desipramine treatment of depression (13). (A comprehensive review is available from I Sakinofsky, unpublished.) Because it is not possible to accurately predict suicide in an individual (14,15), suicidal risk can only be estimated. Several demographic and clinical variables associated with suicide have been identified across psychiatric populations and are discussed in greater detail elsewhere (16). Of these, severe anxiety and agitation are consistently identified as major risk factors in suicide attempts (17–19). The emergence of an unrecognized bipolar disorder with agitation and hypomania, perhaps induced by antidepressants, may also be related to suicidality in adolescents (20). Hence, the potential risks of a medication-induced "activation syndrome" (so named to distinguish these symptoms from akathisia, an extrapyramidal side effect seen with neuroleptic medications), defined as emergent anxiety, hostility, agitation, or suicidality, must be balanced against the potential benefits of an antidepressant. In the following section, we summarize the evidence for these risks and benefits.

Antidepressant Pharmacotherapies: Benefits and Risks

Adults

Benefits. There is ample evidence to support the efficacy of antidepressants for MDD in adult patients (that is, patients aged 18 to 65 years). Many recent systematic reviews have confirmed previous metaanalyses showing that antidepressants are superior to placebo in improving depressive symptoms and increasing clinical response

and remission rates (21,22). This is true for both older medications (for example, TCAs) and newer medications (that is, SSRIs and other novel antidepressants).

Risks. Although suicidality associated with SSRIs has been raised as an issue in early reports and in more recent editorials (3), there is little peer-reviewed evidence to support these claims. A series of analyses of the FDA database of all clinical trials involving newer antidepressants found no significant differences between active medications and placebo in regard to suicide attempts or behaviours (23,24).

Children and Adolescents

Benefits. Unlike the evidence from adult studies, there is less evidence for the benefits of antidepressant medications for depression in children and adolescents. Systematic reviews have shown that TCAs are no better than placebo in pediatric and adolescent depression (25–27). Initial published studies seemed to show that SSRI medications—for example, citalopram (28), fluoxetine (29,30), paroxetine (31), and sertraline (32)—were efficacious, compared with placebo. However, of 15 RCTs funded by pharmaceutical companies, only 6 were published. When the unpublished studies were included, most of the newer antidepressants (that is, citalopram, paroxetine, sertraline, and venlafaxine) were found to be no better than placebo in relieving symptoms of depression; only fluoxetine was consistently found (in 2 studies) to be superior to placebo (33). The magnitude of the benefit for fluoxetine over placebo can be estimated at an excess of 20 to 25 patients responding for every 100 patients treated with medication.

The benefits of antidepressants for children and adolescents must also be evaluated in the context of the limited evidence base for treatments. Systematic reviews have identified some evidence to support the efficacy of psychosocial treatments such as cognitive-behavioural therapy (CBT) for MDD; however, these findings are based on smaller and not-well-controlled trials that usually involve mild-to-moderate depression (27,34,35). In the recent Treatment for Adolescents with Depression Study (TADS), an RCT involving adolescents with more severe depression (n = 439), fluoxetine alone was superior to CBT alone (which, in turn, was not significantly better than placebo), but the best results came from the combination of CBT and fluoxetine (36).

Risks. Some studies included evidence of adverse events with SSRIs, variously described as "emotional lability, hostility and suicidal ideation/gestures" (31). The risk of suicidality was identified as a real issue in the metaanalysis of the 15 published and unpublished RCTs of SSRIs and SNRIs in children and adolescents (33). With the exception of fluoxetine, these studies found higher rates of emergent suicidality, ranging from 2.6% to 7.7%, for the newer antidepressants (that is, citalopram, paroxetine, sertraline, and venlafaxine), compared with 0.6% to 3.8% for placebo (33). Again, only fluoxetine did not show any increase in suicidality relative to placebo (3.6% and 3.8%, respectively) (33). Similarly, in the TADS study, more adverse events were associated with fluoxetine than with placebo, but there were no significant differences in suicide-related adverse events (that is, worsening ideation or increased attempts) (36).

The FDA recently reported an independent reanalysis of pediatric clinical trial data undertaken after all adverse events were reclassified according to strict criteria developed by the Columbia University suicide research group (37,38). Generally, the findings were similar. In all trials for all diagnoses, the risk ratio (RR) of suicidality was significantly higher for non-TCA antidepressants, compared with placebo (RR 1.78; 95%CI, 1.14 to 2.77) (Note that an RR of 1 indicates no difference in risk of an event between 2 conditions, while an RR of 2 indicates twice the risk.) The RR was also significantly higher for all non-TCA antidepressants used in treating MDD (RR 1.71; 95%CI, 1.05 to 2.77). However, the RR for SSRIs in MDD trials was not significantly higher (RR 1.41; 95%CI, 0.84 to 2.37), nor was the RR for fluoxetine (RR 0.92; 95%CI, 0.39 to 2.19). These results show that some risks are associated with antidepressants in these trials but that the results are not consistent across all diagnoses or medications. The magnitude of these risks in children and adolescents can be estimated at perhaps 1 to 3 excess cases of emergent suicidality for every 100 patients treated with a non-TCA antidepressant other than fluoxetine, which carries a lower risk.

Elderly

Benefits. Although fewer RCTs have been conducted in older (aged over 60 years) populations, systematic reviews support the efficacy of antidepressants for treating depression in older adults (39–42) and for treating depression associated with comorbid medical conditions (for example, poststroke), which affects many older patients (43–45).

Risks. Unfortunately, no data analyses exist for older populations with respect to suicidality associated with antidepressants.

Limitations of the Evidence

Systematic reviews are only as good as the studies included. Most RCTs, especially those designed to examine antidepressant efficacy for new drug registration, have limitations that make it difficult to evaluate benefit–risk ratios for clinical populations. For example,

adverse events are often classified according to preexisting categories that may not adequately reflect the events, and these studies are not powered adequately to detect differences in events (such as suicidality) that occur with low frequency. Also, the validity and confidence of systematic reviews to determine benefit–risk assessment is compromised by publication bias, according to which (usually) negative studies remain unpublished. Hence, registration of all clinical trials in a central, public database should be a high priority for the field. Indeed, several influential medical journals have mandated such registration as a precondition to consideration for publication (46).

Additionally, restrictive entry criteria in clinical trials often make it difficult to generalize results to real-world populations. For example, severe symptoms, comorbidity, and acute suicidality are often exclusion criteria for participation in an RCT. Therefore, RCT results should be supplemented by naturalistic studies in large clinical networks, with systematic reporting of outcomes and adverse events. One such example is a carefully designed case–control study that examined suicidal behaviour in patients treated with antidepressants entered in the UK General Practice Research Database (GPRD) (47). The GPRD contained information on 159 810 patients prescribed 1 of the 4 antidepressants studied. Of these, 555 patients who manifested suicidality after initiating an antidepressant were compared with 2062 control subjects. As expected, the risk for suicidality was highest in the first 10 days of starting treatment. However, after other factors known to be associated with suicidality were controlled for, there was no evidence that fluoxetine, paroxetine, or amitriptyline conveyed any significant additional risk of suicidality, compared with the TCA dothiepin (47). These findings also held in the subgroup of patients aged 10 to 19 years. Of note is that no completed suicides were reported in the study cohort aged 10 to 19 years and taking medications. However, among the entire GPRD population during the study period, there were 15 completed suicides in this age group, none of whom were taking antidepressants at the time of death (47). This serves as a stark reminder of the lethal nature of untreated depressive illness in young people.

Summary

The evidence shows that the benefit–risk ratio for newer antidepressants appears to differ among age groups and also among medications. The magnitude of the elevated risk among children and adolescents shown in RCTs (approximately 1 to 3 excess cases of emergent suicidality for every 100 patients treated with antidepressants other than fluoxetine) must be considered relative to any potential benefits of treatment, which have been shown only for fluoxetine (with a benefit magnitude of 20 to 25 excess cases of response). Conversely, large naturalistic studies have not found any increased risk of suicidality associated with fluoxetine or paroxetine use in children and adolescents. Regulatory agencies, however, must balance the evidence with their mandate to protect clinical populations. Thus they take an appropriately conservative approach and have required stricter warnings from manufacturers; they have also advocated for increased clinical attention to possible emergent suicidality with the onset of treatment with all antidepressant medications. Although the risk signal seems higher and the benefit signal lower in younger age groups, it seems sensible to recommend such clinical vigilance in all patients. Finally, it should be noted that, although this review specifically addressed antidepressants used to treat MDD, these medications are also used to treat anxiety and other disorders. The same clinical cautions should apply to their use across all clinical populations.

Clinical Recommendations for Prescribing Antidepressants

1. In adults and in the elderly, there are clear benefits with antidepressants and, in the case of adults, little or no evidence to support any risks for emergent suicidality. Hence, newer antidepressants such as the SSRIs, SNRIs, and novel agents remain first-line treatments for depression in these age groups. [Level 1 evidence]

2. In children and adolescents, there is good evidence for benefit only with fluoxetine. There is also some evidence to support increased risks of suicidality with newer antidepressants, with the exception of fluoxetine. Hence only fluoxetine is considered a first-line treatment for depression in children and adolescents. [Level 1 evidence]

3. In children and adolescents, SSRIs other than fluoxetine can be considered as second-line treatments, especially when the depression is severe, chronic, and associated with comorbid conditions, and (or) psychosocial treatments such as CBT have not worked. SNRIs and other novel agents should be considered as third-line treatments because of their higher adverse event profiles in these populations. [Level 3 evidence]

4. Close monitoring for suicidality is important in patients with depression, especially in the early phases of treatment when suicidal risk is highest. If antidepressants are used, treatment should include prior discussion with the patient (and family if appropriate) of potential side effects that may affect suicidality, such as anxiety (including panic attacks), agitation (including irritability, hostility, and impulsivity), hypomania, and activation syndrome. Early reassessment is indicated when initiating an antidepressant. For example, in children and adolescents,

regular weekly contact (such as appointments or telephone calls) should be scheduled within the first month of prescribing an antidepressant to assess for these adverse events. [Level 2 evidence]

5. Further studies are required to determine specific benefits and risks of antidepressants in age-specific groups, including children, adolescents, and elderly patients. These should incorporate more real-world designs, such as designs evaluating combination medication and psychotherapy treatment vs monotherapies; should examine other populations, such as those with more severe depression and comorbid conditions; and should include longer-term naturalistic studies focusing on systematic evaluation of outcome and adverse events. Further, all clinical trials, whether for pharmacologic, other somatic, or psychosocial treatments, should be registered in a central public registry to ensure that relevant information is available for valid and reliable evaluation of the benefits and risks of treatments for depression and other medical conditions.

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