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**PRESCRIBING ANTIDEPRESSANTS FOR DEPRESSION IN 2005:
RECENT CONCERNS AND RECOMMENDATIONS**

A Statement for the Canadian Psychiatric Association

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BACKGROUND

“Clinical Guidelines for the Treatment of Depressive Disorders,” published by the Canadian Psychiatric Association (CPA) and the Canadian Network for Mood and Anxiety Treatments (CANMAT) in 2001, 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). These recommendations were based on a better tolerability and safety profile of these agents compared to tricyclic and MAO inhibitor agents. For adults, there was Level 1 evidence (meta-analyses or replicated randomized controlled trials [RCTs]) to support these recommendations. In children and adolescents, only Level 2 evidence (at least one RCT) was available to support fluoxetine and paroxetine as first line treatments; in contrast, tricyclic antidepressants were “not recommended” on the basis of Level 1 evidence.

Recently, the safety of SSRIs, SNRIs and other novel agents has been questioned, in regards 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 these 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 tricyclic antidepressants to perform effectively in this population. While several published studies showed significant benefit for SSRIs in children and adolescents, the situation was confounded when it emerged that many other industry-sponsored trials that failed to find significant benefit were unpublished (6). Furthermore, these studies included evidence of significant adverse events that included 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 Several editorials questioned whether these unpublished, negative trials were being deliberately or otherwise concealed or ignored (7).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 United States, the United

Kingdom, and elsewhere, to mandate changes in product labeling 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 regards 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 a number of disorders and conditions, this statement focuses on studies of antidepressants in MDD. The procedure was similar to that for the original guidelines, including the same ratings for Level of Evidence (1). In brief, a literature search was conducted focusing on systematic reviews of RCTs published since 2001. Recent reports from the major government agencies, including the reanalysis of clinical trial data from the U.S. Food and Drug Administration (FDA) that included all known unpublished studies, were also scrutinized. Based on these data, the benefits and risks for prescribing antidepressants in different age groups are summarized, followed by clinical recommendations. The statement was peer-reviewed by external experts in the field and by members of CANMAT.

CLINICAL ISSUES IN EVALUATING SUICIDALITY

Before reviewing the relationship 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. Antidepressants are also usually prescribed to people when their symptom severity (including suicidality) is highest, so 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 (e.g., breakup of a relationship), 4) a specific adverse

event associated with the antidepressant, or 5) a non-specific adverse event (e.g., increase in anxiety or agitation) associated with the antidepressant.

Although the newer antidepressants have been the focus of attention recently, some of these concerns predate the SSRI era. For example, emergent or exacerbated suicidal ideation was described during desipramine treatment of depression (13) (for a comprehensive review, see (14)). Because accurate prediction of suicide in an individual is not possible (15,16), suicidal risk can only be estimated. A number of demographic and clinical variables that are associated with suicide have been identified across psychiatric populations and are discussed in greater detail elsewhere (14,17). Of these, severe anxiety and agitation are consistently identified as major risk factors in suicides and attempts (18-20). The emergence of an unrecognized bipolar disorder with agitation and hypomania, perhaps induced by antidepressants, may also be related to suicidality in adolescents (21). Hence, the potential risks of a medication-induced “activation syndrome” (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, the evidence for these risks and benefits is summarized.

ANTIDEPRESSANT PHARMACOTHERAPIES – BENEFITS AND RISKS

Adults

Benefits: There is ample evidence to support the efficacy of antidepressants for MDD in adult (18-65 years old) patients. Many recent systematic reviews have confirmed previous meta-analyses showing that antidepressants are superior to placebo in improving depressive symptoms and increasing clinical response and remission rates (22,23). This is true for both older medications (e.g., tricyclic antidepressants) and newer medications (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 suicide attempts or behaviours (24,25).

Children and Adolescents

Benefits: Unlike the situation in adults, there is less evidence for the benefits of antidepressant medications for depression in children and adolescents. Systematic reviews have shown that tricyclic antidepressants are no better than placebo in paediatric and adolescent depression (26-28). Initial published studies seemed to show that SSRI medications, e.g., citalopram (29), fluoxetine (30,31), paroxetine (32), and sertraline (33), were efficacious compared to placebo. However, only 6 of 15 RCTs funded by pharmaceutical companies were published. When the unpublished studies were included, the majority of newer antidepressants (citalopram, paroxetine, sertraline, 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 (34). The magnitude of the benefit for fluoxetine over placebo can be estimated at an excess of 20-25 patients responding for every 100 patients treated with medication.

The benefits of antidepressants in children and adolescents must also be evaluated in the context of the limited evidence base for treatments. Systematic reviews have identified that psychosocial treatments such as cognitive-behavioral therapy (CBT) have some evidence to support efficacy in MDD, but these findings are based on smaller and not well-controlled trials that usually involve mild to moderate depression (28,35,36). In the recent Treatment for Adolescents with Depression study (TADS), an RCT with more severely depressed adolescents (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 (37).

Risks: Some studies included evidence of adverse events with SSRIs variously described as “emotional lability, hostility and suicidal ideation/gestures” (32). The risk of suicidality was identified as a real issue in the meta-analysis of the 15 published and unpublished RCTs of SSRIs and SNRIs in children and adolescents (34). With the exception of fluoxetine, these studies found higher rates of emergent suicidality ranging from 2.6% to 7.7% for the newer antidepressants (citalopram, paroxetine, sertraline, venlafaxine) compared to 0.6% to 3.8% for placebo (34). Again, only fluoxetine did not show any increase in suicidality relative to placebo (3.6% vs. 3.8%, respectively) (34). Similarly, in the TADS study, there were more adverse events associated with fluoxetine than placebo, but there were no significant differences in the suicide-related adverse events (worsening ideation or attempts) (37).

The FDA recently reported an independent re-analysis of paediatric clinical trial data after reclassifying all adverse events using strict criteria developed by the Columbia University suicide group (38,39). Generally, the findings were similar. In all trials for all diagnoses, the risk ratio (RR) [95% confidence interval] of suicidality was significantly higher for non-TCA antidepressants compared to placebo (1.78, [1.14-2.77]) [note that a RR of 1 indicates no difference in risk of an event between two conditions, while a RR of 2 indicates twice the risk]. The RR was also significantly higher for all non-TCA antidepressants in MDD (1.71, [1.05-2.77]). However, the RR for SSRIs in MDD trials was not significantly higher (1.41 [0.84-2.37]), nor was the RR for fluoxetine (0.92, [0.39-2.19]). These results show that there are some risks 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 an SSRI other than fluoxetine, which carries a lower risk.

Elderly

Benefits: Although there are fewer RCTs conducted in older (>60 years old) populations, systematic reviews support the efficacy of antidepressants for older adults with depression (40-

43) and for depression associated with comorbid medical conditions, such as following stroke, which affect many older patients (44-46).

Risks: Unfortunately, there are no analyses of data for older populations in 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 pre-existing 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 in 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, and several influential medical journals have mandated such registration prior to consideration for publication (47).

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, results of RCTs 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 in the UK General Practice Research Database (GPRD) (48). The GPRD contained information on 159,810 patients prescribed one of the four antidepressants studied. Of these, 555 cases that manifested suicidality after initiating an antidepressant were compared to 2062 controls. As expected, the risk for suicidality was highest in the first 10 days of starting treatment. However, after controlling for other factors known to be associated with suicidality, there was no evidence that fluoxetine,

paroxetine or amitriptyline conveyed any significant *additional* risk of suicidality compared to the tricyclic antidepressant, dothiepin (48). These findings also held in the subgroup of patients aged 10-19 years old. Of note is that no completed suicides were reported in the 10-19 year old study cohort that was taking medications. However, there were 15 completed suicides in this age group in the entire GPRD population during the study period, none of whom were taking antidepressants at the time of death (48). 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 be different for different age groups and also between different medications. The magnitude of the elevated risk in children and adolescents 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 magnitude of benefit of 20 to 25 excess cases of response). In contrast, large naturalistic studies have not found any increased risk of suicidality with fluoxetine or paroxetine in these age groups. Regulatory agencies, however, must balance the evidence with their mandate for protection of clinical populations. Thus, they take an appropriately conservative approach, and have mandated stricter warnings from manufacturers and advocated for increased clinical attention to the possibility of 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 addressed antidepressants specifically for the treatment of MDD, these medications are also used for the treatment of 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 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, associated with comorbid conditions, and/or when psychosocial treatments such as CBT have not worked. SNRIs and other novel agents should be considered as third-line treatments due to their higher adverse event profiles in these populations. [Level 3 evidence]
4. Close monitoring for suicidality in depressed patients is important, especially in the early phases of treatment when suicidal risk is highest. If antidepressants are used, this 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 (akathisia). Early reassessment is indicated when initiating an antidepressant. For example, in children and adolescents, appointments or telephone contacts should be scheduled at least weekly 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 studies should incorporate more real-world designs, such as evaluating combination medication and psychotherapy treatment vs. monotherapies, examine other populations, such as more severe depression and comorbid conditions, and include longer-term naturalistic studies focusing on systematic evaluation of outcome and adverse events. Furthermore, all clinical trials, whether

for pharmacological, 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 benefits and risks of treatments for depression and other medical conditions.

DISCLOSURES

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