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Editorial

Antidepressants from a public health perspective: re-examining effectiveness, suicide, and carcinogenicity

Introduction

The widespread use of antidepressants has rarely been critiqued from a public health perspective. It is as although the medical profession has felt that depression in the community at large could be resolved by the widespread diagnosis of major depressive disorder (MDD) in people with depressive symptoms and subsequent prescription of antidepressant medication. This broad approach to diagnosis and treatment grows out of the medical approach to illness. In this editorial, we examine the need for a public health approach to the prevention and treatment of depression, as well as a better understanding of the valid role of antidepressants in such treatment.

Diagnosis

In clinical psychiatry, the diagnosis of depression is usually given to people who have severe recurrent episodes of depression, conceived as a syndrome of multiple physical as well as psychological symptoms (1). Traditionally, from the late 19th century until 1980, when the psychiatric nosology was revised to the current approach first defined in DSM-III, depression as a disease was identified in three categories: manic depressive illness (MDI), melancholia, and neurotic depression. MDI meant recurrent severe depressive or manic episodes. Melancholia meant severe depressive mood with marked psychomotor retardation, anhedonia, and a complete lack of change in mood even with positive environmental circumstances. Neurotic depression involved mild-to-moderate chronic anxiety with depression, without a highly recurrent course (as in manic depression), without marked psychomotor retardation (as in melancholia). The melancholic subtype of depression is currently included in DSM-IV and ICD-10, but the concept of depression has been widened to include all kinds of depressive symptoms including: chronic mild to moderate depression, anxiety, agitated depression, and highly reactive and labile mood presentations. In the old MDI concept, the presence of depression vs. mania was irrelevant to diagnosis (1). What was relevant was the course of illness consisting of any repeated severe mood episodes alternating with periods of normal mood or markedly decreased mood symptoms. The current major depressive disorder (MDD) definition ignores this course: the presence of depression is all that is needed, and the course of illness can be recurrent, as in the original MDI concept with periods of normal mood, or highly chronic, as is perhaps the case with the majority of patients currently receiving the MDD diagnosis. Furthermore, the MDD concept implies that depression is a homogeneous entity, whereas for a century, this has been an unresolved matter: Is depression one thing or many (2,3)?

Treatment Studies

It is possible that the disparate nature of this MDD category has led to a state where a potential biological disease characterized by depression, such as MDI, is mixed with many other depressive symptom presentations which are not owing to a biological disease of depression, such as solely psychosocially caused depressive symptoms. The possibility that such a broad mixture of different depressive causes may be incorporated into the MDD category is suggested by the increasing evidence that antidepressant medications, which may be effective for the biological disease of depression, appear to be decreasingly effective in our current MDD definitions (4–6), with markedly heterogeneous results in a long-term basis (7, 8).

As has been widely discussed in the lay media, some reanalyses of the FDA database of antidepressants trials indicate that these medications are not much more effective than placebo (4). Although presented in a way to suggest almost no

benefit at all, a more statistically accurate interpretation of those data indicate that antidepressants are more clearly effective in moderate-to-severe acute depressive episodes, as opposed to mild episodes (9). Moreover, some explanation for the apparently modest clinical effect of antidepressants could be found in how depressive episodes are measured and how unreliable symptoms scales could be, reflecting in turn the heterogeneity of the underlying construct (10).

The evidence from the large FDA database is limited to short-term effects for acute depressive episodes, usually meaning about 2 months in duration. Most patients take antidepressants for years, and, given a limited randomized literature on that topic (11), the best evidence probably comes from the largest relevant study: the NIMH-sponsored study of MDD treatment with antidepressants called STAR*D (Sequenced Treatment Alternatives for Resistant Depression) (12). In this study, over 3000 patients were initially treated with the serotonin reuptake inhibitor (SRI) citalopram. The patients that did not respond were then treated with other antidepressants either alone or in combination with the first antidepressant. Those patients who failed to respond to the second level of treatment were treated with older antidepressants, such as tricyclic antidepressants, and the final level of treatment (the non-responders to the other medications) received our most potent medications such as monoamine oxidase inhibitors (MAOIs). In this study, the overall cumulative acute response was reasonable, approximating 60–70%. However, researchers who conducted that study rarely emphasize that about 40–50% of those individuals who initially responded acutely for severe depression with antidepressants did not stay well despite continuing their antidepressants for up to 1 year, relapsing into new major depressive episodes. Thus, the cumulative remission rate with all the antidepressants at our current disposal at 1 year of follow-up was in the 30% range, rather than the 60–70% range (13). This is a markedly lower rate of long-term benefit with antidepressants than has commonly been cited and believed.

Another part of the research literature that suggests limitations to benefit with antidepressants is based on another large NIMH-sponsored study called STEP-BD (Systematic Treatment Enhancement Program for Bipolar Disorder) (14), in which antidepressants were used in acute bipolar depression, added to standard mood stabilizers. In a randomized double-blind placebo controlled trial, they were found to be equivalent to placebo (15). This study completely contradicts most clinicians' views, and the practice of widespread antidepressant usage in bipolar depression. A large literature exists with controversy around this topic (16), but STEP-BD is by far the largest and best-designed study addressing this question, and it clearly is on the side of inefficacy of antidepressants in bipolar depression.

Thus, antidepressants are less effective in MDD than previously believed according to our best recent data, especially in the long term, and they are ostensibly ineffective in bipolar depression. The traditional analogy of antidepressant usage for depression to insulin usage to diabetes may be wrong-headed: Depression is not a single disease entity even if polyfactorial and chronic like diabetes, and antidepressants do not have marked long-term benefits as insulin does in diabetes; rather, antidepressants should be analogized to antibiotics, with their marked acute benefit for severe episodes, but lack of benefit when continued long term. Furthermore, they are completely ineffective for some kinds of depression, as in bipolar illness.

Suicide

The previous studies, throwing some doubt as to the benefit of antidepressants in depressive illness, may help us understand why there is paradoxical evidence that antidepressants may increase the risk of suicide. The evidence of such risk is based on meta-analyses of RCTs available to the Food and Drug Administration (FDA), in which the increased overall suicidal ideation or suicide attempt rate with antidepressants is 2.4% vs. 1.4% with placebo (relative risk 1.65, 95% confidence intervals 1.07–2.55). The FDA has been criticized by child psychiatrists for not taking into account actual suicides, as there were no completed suicides in those RCTs. The NIMH-sponsored Treatment for Adolescents with Depression (TADS) study was designed to look at suicidality more carefully (17). In this study, 439 adolescents (age 12–17) were treated with fluoxetine vs. cognitive-behavioural therapy (CBT) vs. the combination vs. placebo: 5.5% overall had suicide related adverse events, meaning increased suicidal ideation or suicide attempts. However, again, the researchers who conducted that study de-emphasized the frequency of suicidal outcomes, and used p-values inappropriately, concluding from statistical non-significance that there was no association when the study was not powered to assess low frequency side effects, a methodological problem we have previously emphasized (18). We reanalyzed the TADS data descriptively, and found notable evidence of

increased suicide risk in the fluoxetine arms of that study. Six of seven suicide attempts occurred in patients on fluoxetine, producing a relative risk of 6.19 (95% confidence intervals 0.75–51.0). Although again there were no actual suicide deaths in that study, the rare occurrence of suicide deaths is important to keep in mind and the association of suicide attempts as a major risk factor for suicide death cannot be ignored (17).

William Osler, the great late 19th century physician, once said that the art of medicine is the art of balancing probabilities (19). Here, we present for the first time in a systematic manner, an analysis of the risk of causing suicide with SRIs vs. the rate of preventing suicide with SRIs.

It is generally estimated that about 8% of those who attempt suicide eventually complete suicide (17). Some judgments can be made about the potential risk of suicide with antidepressants when one takes into account such evidence: the number needed to harm (NNH) for suicide adverse events in the TADS study was 19; for suicide attempts, 11.6; and 8% of suicide attempts were lethal, the NNH for suicide deaths was 535. The number needed to treat (NNT) for antidepressant efficacy in TADS was 3.9. If one tries to convert that efficacy into a prevention of suicide rate, one might calculate as follows: There are about 500 000 suicide attempts per year in the United States (US) among adolescents, and 2000 suicides (17). Thus, the suicide rate per attempt is 0.4%. If one presumes that the lifetime suicide rate in MDD is 2.4% (17), and about one-third occurr during young adulthood, then the NNT to prevent one suicide with antidepressants, based on TADS, is 560.

Thus, with a NNH for suicide of 535 and a NNT for suicide prevention of 560, one can see that this controversy reflects an equalization of harm and benefit such that antidepressants can be said to be, at the population level, neutral in their effects on suicide.

One risk factor for children and adolescents developing suicidality on antidepressants is the frequency of bipolar disorder among this group. Before manic episodes occur, patients often have depression. The diagnosis of MDD in depressed children and adolescents is always provisional because 40–50% of those patients later develop mania in 10–15-year follow-up based on studies of 12-year-old children and a separate study of 23-year-old adults (20, 21). One reason why adolescents and young adults may be at special risk of suicidality with antidepressants could be misdiagnosed bipolar depression because antidepressants can cause mixed manic episodes, which are highly associated with suicidality (17).

Carcinogenicity

As is well known (22, 23), estrogen hormone replacement therapy was associated with previously underappreciated and unrecognized carcinogenic risks which occurred in a small percentage of patients who received the treatment. However, as the treatment was given to a very large number of individuals in the community, that small percentage of increased risk was clinically important. One cannot say for certain whether a similar risk may not be present with antidepressants. Regarding carcinogenicity for instance, the majority of antidepressants are carcinogenic in animal studies (24). Human studies of carcinogenic risk are few and epidemiological, and therefore liable to confounding bias. Most of these studies do very little to correct for potential confounding factors. With that caveat, a meta-analysis of these studies finds a small association between antidepressants and increased risk of breast cancer (25). Many have criticized that meta-analysis on the basis of confounding factors and such criticism may be valid. Even so, the clinical community needs to ask itself a question: should we assume that all antidepressants are safe until proven otherwise? Or should we presume that they are harmful as all drugs are, until safety is proven? (26)

A public health approach

To summarize, antidepressants have been shown to be much less effective in clinical practice than previously believed. This does not entail complete lack of efficacy, nor does it affirm conspiracy theories related to the pharmaceutical industry. Instead, it may be relevant that our diagnostic definitions of MDD are too diverse. Furthermore, antidepressants seemingly have notable risks including a small but real increased risk of suicide, and a possible small increased risk of cancer. Given all of the above, the common usage of antidepressants for depressive symptoms in the community is debatable.

What would a public health approach be? A public health approach involves focusing on prevention rather than treatment, as is traditionally the case. Questions that need to be asked include what are risk factors for depressive symptoms and major depressive episodes and how can we prevent those risk factors (27). Interventions aimed at reducing the frequency of risk factors are in order

and increased social work and other interventions for childhood trauma need to be reviewed.

Risk factors for recurrent severe mood episodes, as in bipolar disorder, have begun to be delineated. These include a number of genetic and environmental factors including possible intranatal uterine infections (28). These early environmental insults could be addressed by improved prenatal care, and social and medical interventions to enhance medical care of individuals during pregnancy. Furthermore, the potential neurotoxic effect of amphetamines (29) and the worsening impact of antidepressants in bipolar disorder (16) might be risk factors for developing more severe mood disorders in individuals exposed to amphetamines or antidepressants in childhood.

Interventions in adulthood may help in terms of immediate risk factors for new depressive episodes (30, 31). Social isolation has been associated with markedly worse outcomes in depression and bipolar disorder (32). Increased social support through advocacy and support groups may be helpful with that risk factor (33). Additional funding for proven psychosocial interventions to assist with the course of mood disorders would also be important.

This public health approach is not at odds with pharmacotherapy; it should be complementary. It would lead to using drugs more effectively, especially in more severe mood episodes, and more acutely, as with antibiotics, rather than in a chronic and complacent manner as has been the case in the past. The public health approach is both more scientific and more ethical, avoiding stigmatization by broad diagnostic labels (34) and focusing on risk factors that all of the population potentially can possess.

Summary

Although antidepressant medications have been shown to improve acute severe symptoms associated with the biological disease of depression, research indicates that they do not appear to be useful for our current MDD definitions. We believe the current broad DSM-IV/ICD-10 diagnosis of MDD hinders clinicians' selectiveness in prescribing antidepressants. The heretofore rarely criticized broad concept of MDD needs to be reevaluated after 30 years of being largely untouched, as it mostly remains in proposals for DSM-5 and ICD-11.

In addition to their limited efficacy, risk factors associated with antidepressant treatment suggest a need for alternate and/or concomitant means of preventing and treating depression. Given the vast number of people that suffer from depression, treatment options and risk should be assessed in the population as a whole in the broader context of prevention. Efforts to identify and combat risk factors related to depression may help to decrease reliance on pharmacotherapy with antidepressants, an intervention that research suggests may confer limited benefits while associated with significant risks. Preventive health efforts ranging from prenatal care to psychosocial interventions lasting into adulthood may work in tandem with pharmacotherapy to improve treatment outcomes in those at risk for depression.

We conclude that a public health approach should be adopted in the prevention and treatment of depression, and may allow for more effective use of antidepressant medication.

Declaration of Interest

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