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Are SSRI Antidepressants Little More than Active Placebo? A Critical Exploration.

Elia Abi-Jaoude, MSc, MD, FRCPC*

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"I know that most men, including those at ease with problems of the greatest complexity, can seldom accept even the simplest and most obvious truth if it be such as would oblige them to admit the falsity of conclusions which they have delighted in explaining to colleagues, which they have proudly taught to others, and which they have woven, thread by thread, into the fabric of their lives." Leo Tolstoy

If a physician gives a selective serotonin reuptake inhibitor (SSRI) medication to a patient suffering from mood problems, chances are the patient will feel better. Likewise, if the physician gives a placebo pill to a patient suffering from the same difficulties, chances are the patient will feel better. Physicians who treat depression have extensive experience with the former situation, but little overt experience with the latter.

It is thus no wonder that the results of a string of recent meta-analyses questioning the relative efficacy of SSRIs in comparison to placebo (Kirsch et al., 2002; Turner et al., 2008; Kirsch et al., 2008; Barbui et al., 2008; Fournier et al., 2010)—particularly when unpublished studies were included—are not easy to accept for many physicians. Furthermore, some interpretations and potential implications of these results leave a number of questions unanswered. The present article explores and attempts to come to a resolution around some of these outstanding issues.

Perhaps the most provocative interpretation emanating from the meta-analyses is that the small, statistically significant difference between SSRI and placebo—approximately 2 points overall on the Hamilton Depression Rating Scale (HDRS; full range is 50 and 62 points for the 17-item and 21-item versions, respectively) in one of the earlier studies (Kirsch et al., 2002)—is likely the result of breaking of the blind due to side effects in the SSRI group (Kirsch, 2011). Indeed, trial participants can often tell whether they have been assigned to the drug or placebo group (Rabkin et al., 1986), and randomized controlled trials (RCTs) do not routinely verify or report how well the blind was preserved. Importantly, evidence shows that side effects correlate with response in antidepressant trials (Thomson, 1982; Greenberg et al., 1994).

Reporting greater drug effects, a meta-analysis based on antidepressant studies submitted for approval in Sweden used treatment response, as defined by at least 50% reduction in HDRS scores, as the main outcome measure (Melander et al., 2008). Furthermore, the investigators had access to full study reports and they excluded only one study due to missing data. Response rates were 49% for antidepressant and 33% for placebo (Melander et al., 2008). Given the small differences in average HDRS scores based on the other meta-analyses, however, one would expect that significant levels of symptom reduction in the drug group

* *Research Fellow, Department of Psychiatry, University of Toronto*

email: elia.abi.jaoude@utoronto.ca

(based on HDRS scores) would be counter-balanced by similar levels of symptom *increase* in that group as well. Thus, these findings raise the possibility that some patients became substantially worse on antidepressant.

Nevertheless, the overall effect size of a drug intervention may be underestimated by the placebo-controlled trial design. There is intriguing evidence to suggest that the presence of a placebo comparator in a study can influence the expectancy of participants in a manner that gives an advantage to placebo and puts the drug intervention at a disadvantage. A meta-analysis found that antidepressant response rates were higher in trials where both arms included active drug treatment compared to trials that included a placebo group (Sneed et al., 2008). The findings are consistent with those from two other meta-analyses, which also found that placebo response was higher in studies where participants had a lower chance of being randomized to a placebo group (Papakostas & Fava, 2009; Sinyor et al., 2010). In other words, the expectation of being in an active treatment group appears to improve response rates for trial participants across treatment arms, whereas the presence of a placebo group tends to diminish response in those receiving active drug intervention. Of relevance, a recent survey found that respondents expected a higher likelihood and magnitude of improvement were they to take part in a trial with two active treatment groups as opposed to one with a placebo control (Rutherford et al., 2009). According to a subsequent small pilot antidepressant study, subjects randomized to an SSRI-versus-SSRI track (with no placebo control group) expected a higher magnitude of improvement than did subjects randomized to a placebo-controlled track (Rutherford et al., 2010). Further research is still required to decipher any direct influence of such differential expectancies on actual outcomes.

Another recently-noted factor that may negatively impact response to SSRIs is concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs)—a very commonly-used group of medications, many of which are available over the counter (Warner-Schmidt et al., 2011). After finding a reduced SSRI effect in a rodent model of depression, investigators examined the effect of NSAIDs on remission rates with citalopram in the STAR*D† study, a large, NIMH‡-sponsored antidepressant trial (Trivedi et al., 2006). They found that remission rates were significantly lower in patients on NSAIDs (Warner-Schmidt et al., 2011). Of course, whether or not NSAIDs influence placebo responses in antidepressant trials remains unknown. Still, the NSAID attenuation of antidepressant effects in the animal model appeared to be mediated specifically through inhibition of SSRI-induced inflammatory cytokine increases in the frontal cortex of the brain (Warner-Schmidt et al., 2011). Hence, it is possible that a similar interaction between NSAIDs and placebo might not occur.

It is also worth considering the issue of depression-severity. A number of meta-analyses investigated the effect of baseline HDRS scores, and most of these have identified a divergence between SSRI and placebo in patients with very severe depression (Khan et al., 2002; Kirsch et al., 2008; Fournier et al., 2010). This effect, while statistically significant, ranged in magnitude from small (Kirsch et al., 2008) to medium in the meta-analysis that did not include unpublished studies (Fournier et al., 2010). Of note, the meta-analysis by the European group found no relation between baseline severity and response rate, which was the outcome measure in that study (Melander et al., 2008).

Interesting differences exist among the different meta-analyses in how drug and placebo performed across severity ratings. For example, in one meta-analysis, placebo response decreased while SSRI response remained the same with increasing initial depression severity (Kirsch et al., 2008); whereas in another study both SSRI and placebo showed greater improvement with increasing depression severity, with an interaction favouring the SSRI (Fournier et al., 2010). Nevertheless, the overall results of these meta-analyses are consistent with those of studies showing that trials with more severely depressed patients showed larger

† Systematic Treatment Alternatives to Relieve Depression

‡ National Institute of Mental Health

differences between antidepressant and placebo (Khan et al., 2004; Khan et al., 2005; Khin et al., 2011).

The evidence from these meta-analytic studies casts serious doubt on the utility of SSRIs for mild or moderate depression. Nevertheless, it appears that there is a clinically significant, albeit perhaps small, benefit from SSRI relative to placebo for the acute treatment of very severe depression. Kirsch and others suggest that this difference may arise simply as a result of stimulant and/or sedative effects of SSRIs as opposed to specific antidepressant effects. Indeed, in the versions of the HDRS most commonly used in SSRI trials, the so-called vegetative symptoms (such as decreased sleep and low energy) are over-represented (Zimmerman et al., 2005). As such, HDRS scores can improve when, for example, patients sleep more or experience increased energy, even if there is no change in actual mood symptoms.

From a neurobiological perspective, the long-held belief that depletion of serotonin and other monoamine neurotransmitters causes depressed mood is now in question (Ruhe et al., 2007; Baumeister et al., 2003), as is the impact on mood of increasing serotonin via administration of the precursor tryptophan (Silber & Schmitt, 2010). According to the authors who carried out a meta-analysis of the depletion studies, it "certainly cannot be concluded [that] MDD is *caused* by low levels of 5-HT (serotonin) . . ." (Ruhe et al., 2007). More recent popular theories suggest that neurotrophic factors are actual mediators of depression-related brain changes, and that SSRI action can reverse these changes. However, such findings are nonspecific and far from definitive at this time (Belmaker & Agam, 2008).

Functional magnetic resonance imaging (fMRI) under the so-called resting state has shown increased connectivity between dorsomedial prefrontal cortex (dmPFC) and certain cognitive and affective brain networks in depressed individuals—presumably a reflection of rumination and excessive self-focus (Sheline et al., 2010). SSRI administration to healthy volunteers resulted in decreased functional connectivity between dmPFC and the hippocampus (McCabe et al., 2011). Further, in one fMRI study, subjects were presented with masked faces (i.e., for a duration too short to be consciously perceived), and the investigators analyzed the signal in the amygdala—a brain region involved in emotional arousal (Victor et al., 2010). In contrast to what was seen in healthy controls, the amygdala showed greater response to sad versus happy faces in depressed subjects, and this was reversed after administration of an SSRI; there was, however, no placebo intervention (Victor et al., 2010). The latter point highlights an important limitation, many of the brain changes seen in functional neuroimaging studies, previously attributed to SSRI response, also occur in response to placebo (Mayberg et al., 2002).

Another recent hypothesis comes from a series of neuropsychological studies. These demonstrate that depressed individuals have a negative bias on tasks of facial emotion recognition, emotion categorization and emotional memory; and that healthy volunteers given SSRIs show the opposite pattern (Harmer et al., 2009a). Nevertheless, these are early findings that involve much speculation, including comparisons between depressed individuals and healthy volunteers given SSRIs. In one double-blind study, depressed patients given a single dose of reboxetine—a selective norepinephrine reuptake inhibitor—showed a reversal of the negative emotional processing bias seen in those who received placebo (Harmer et al., 2009b). However, one cannot help but question the clinical validity of such studies given that reboxetine was found ineffective for the treatment of depression in a meta-analysis that included unpublished studies (Eyding et al., 2010).

There are arguments that the most significant difference between SSRI and placebo manifests not in acute treatment but rather in maintenance treatment to prevent relapse. This is supported by two systematic reviews (Geddes et al., 2003; Furukawa et al., 2007) and two meta-analyses (Hansen et al., 2008; Williams et al., 2009), all of which identified much

higher rates of relapse in patients on placebo compared to those on SSRIs. Notably, these studies do not consider the confounding effect of SSRI withdrawal in patients switched from SSRI to placebo. According to one of the meta-analyses, "The most common trial design was an open-label acute treatment phase of six to 15 weeks, followed by a randomized, double-blind, placebo-controlled continuation phase, maintenance phase, or both for acute-phase responders or remitters" (Hansen et al., 2008). Thus, at least a portion of the apparent relapse rates occurring in patients switched from SSRI to placebo is likely related to withdrawal symptoms.

Indeed, a meta-analysis of maintenance trials in which respective responders to antidepressant and placebo were allowed to continue on the same intervention they had responded to in the acute phase showed a much smaller difference in relapse rate between drug and placebo: 79% of placebo responders remained well, in comparison to 93% of antidepressant responders (Khan et al., 2008). Furthermore, preliminary findings from a review of 16 relapse-prevention studies suggests that the majority of patients that relapsed after being switched to placebo did so within the first six months, after which there was no difference in relapse rate between antidepressant and placebo (Laino, 2010). One of the investigators suggested that tapering of SSRI drugs should be carried out much more gradually (such as by "10% [of the dose every] six weeks") than is typically done (Laino, 2010).

Given the long and extensive clinical experience in using SSRIs, one might question the degree of relevance of randomized-controlled trials to real-world effectiveness. For instance, the close attention and follow-up that trial participants typically receive may result in an inflated placebo response that may obfuscate the drug effect. To explore this question, it is instructive to consider outcomes from the STAR*D study—a large pragmatic trial that did not have placebo arms. Initial remission rates to open-label citalopram were about 30% (Trivedi et al., 2006). Patients who did not respond went through subsequent levels that entailed switching or augmentation until they achieved response (at least 50% reduction in symptom scores) or remission (HRSD scores of no greater than 7). A widely discussed result was that, after four levels, the cumulative remission rate was 67% (Gaynes et al., 2009). This remission rate drops to 51%, though, when one includes drop-outs due to side effects (Ghaemi, 2008b). Importantly, only about half of these patients maintained benefit at one year, for an overall long-term remission rate of 25% (Ghaemi, 2008b).

Thus, the effectiveness of SSRIs for depression, considered from a wide range of angles, is not quite encouraging. Nevertheless, the overall evidence suggests potential usefulness of these agents in very severe depression. The benefit in this category may be of greater magnitude than what most of the meta-analyses indicate, due to underestimated drug-treatment effect size in placebo-controlled trials and confounding effects of NSAIDs on antidepressant effects. Moreover, in contrast to average HDRS scores as the outcome measure, response rates point to a clearer separation between SSRIs and placebo. Another possibility is that only a subgroup of those with very severe depression benefit, while others either do not benefit or get worse. These considerations point to a pressing need for efforts to identify those most likely to benefit.

In the meantime, the widespread and often long-term use of these agents needs to be reconsidered. This is particularly worrisome given the limited knowledge of side effects with long-term treatment (Furukawa et al., 2007). Of further concern is the suggestion that some patients exposed to long-term antidepressants drugs may experience worse mood and related symptoms in the long run, possibly through tachyphylactic effects (Fava & Offidani, 2010; El-Mallakh et al., 2011).

There have been increasing concerns raised about the ever-broadening definition of

clinical depression (Ghaemi, 2008b; Moncrieff, 2008; Horwitz & Wakefield, 2007), as well as the adoption of simplistic biological models regarding treatment (Lacasse & Leo, 2005). It appears that highly aggressive marketing, including systemic manipulation of antidepressant studies and literature (Ioannidis, 2008; Jureidini et al., 2008; Spielmans & Parry, 2010) is a driving force behind these issues.

The reality regarding current knowledge and treatments is humbling. SSRIs and other drugs considered as antidepressants may be little more than crude tools which impact the brain in ways that are not well understood (Moncrieff & Cohen, 2006). Nevertheless, by maintaining a critical, cautious and judicious approach to diagnoses and treatment (Ghaemi, 2008a; Schiff et al., 2011), one can work with patients in a transparent and cooperative manner to help relieve suffering and avoid doing harm.

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