

# Possible role of more positive social behaviour in the clinical effect of antidepressant drugs

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Increasing serotonin decreases quarrelsome behaviours and enhances agreeable behaviours in humans. Antidepressants, even those whose primary action is not on serotonin, seem to increase serotonin function. We suggest that antidepressants act in part by effects on social behaviour, which leads to a gradual improvement in mood. We review the evidence supporting the idea that antidepressants may be moving behaviour from quarrelsome to agreeable. The more positive social responses of interaction partners would initiate a cycle of more positive social behaviour, and this iterative process would result in a clinically significant improvement in mood.

## Introduction

Two important characteristics of antidepressant drugs are that they are not as effective as an ideal antidepressant would be, and there is a delay in their maximal effect. A biological mechanism proposed for the delay in onset of antidepressants is that different classes of antidepressants, whatever their primary neurotransmitter target, cause slow changes in pre- or postsynaptic mechanisms that increase serotonin function, which is then responsible for the improvement in mood.<sup>1</sup> Another proposed mechanism is based on a cognitive neuropsychological model and suggests that antidepressants “change the relative balance of positive to negative emotional processing,” which results in later changes in mood.<sup>2</sup> The purpose of this commentary is to suggest another mechanism involving serotonin-induced changes in social behaviour that, over time, will improve mood. First, the background information on how serotonin and antidepressants can influence social behaviour is presented. Then, we examine the idea that improved social interactions may play a role in the clinical effect of antidepressants.

## Serotonin and social behaviour in animals and humans

Aggression is one of the more dramatic aspects of social behaviour. The role of serotonin in regulating aggression has been studied extensively in experimental animals. A meta-analysis of the effect of altering serotonin in a variety of different species, tested using different models, concluded that serotonin “has an overall inhibitory effect on aggression.”<sup>3</sup> In vervet monkeys, lowering serotonin using acute tryptophan depletion<sup>4</sup> or by giving the tryptophan hydroxylase inhibitor p-chlorophenylalanine<sup>5</sup> increased aggression. On the other hand, increasing serotonin with tryptophan or the selective serotonin reuptake inhibitor (SSRI) fluoxetine increased the behaviour of approaching other animals and grooming them.<sup>5,6</sup> This suggests that serotonin may alter social behaviour along the continuum from agonistic to affiliative. A number of studies suggest this may also be true in humans.

Acute tryptophan depletion increases human aggressive responses and decreases affiliative behaviour in many laboratory tests.<sup>7</sup> Conversely, tryptophan supplements may decrease aggression and increase positive social behaviour. Twelve

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*J Psychiatry Neurosci* 2014;39(1):60-5.

Submitted Aug. 6, 2013; Revised Sept. 25, 2013; Accepted Oct. 1, 2013.

DOI: 10.1503/jpn.130165

aggressive inpatients with schizophrenia were given tryptophan and placebo, each for 4 weeks, in a double-blind crossover study.<sup>8</sup> Tryptophan decreased the number of incidents on the ward requiring intervention. In another double-blind study comparing 10 aggressive patients receiving tryptophan with 10 inpatients receiving placebo, tryptophan decreased the need for injections of antipsychotics and sedatives to control agitated or violent behaviour.<sup>9</sup> In a placebo-controlled study on premenstrual dysphoric disorder (PMDD), tryptophan caused a significant decline in irritability, the mental state associated with agonistic interactions.<sup>10</sup> The effect of tryptophan, relative to placebo, was compared in 2 crossover studies on healthy participants, using ecological momentary assessment to investigate their social behaviour in everyday life. Participants repeatedly checked off, on a list, behaviours they displayed during social interactions lasting more than 5 minutes throughout many days.<sup>11</sup> One of the measures obtained was social behaviour along an agreeable–quarrelsome dimension. While behaviours along this dimension vary from one interaction to another, mean values based on at least 70 interactions show considerable temporal stability.<sup>12</sup> In the first study, tryptophan, relative to placebo, decreased quarrelsome behaviours.<sup>13</sup> There was no effect on agreeable behaviours, but this may have been a ceiling effect, as agreeable behaviours are usually more common than quarrelsome ones. This idea was tested in a second study that was similar to the first except that the participants were psychiatrically healthy but they were in the upper levels of the population distribution for irritability.<sup>14</sup> In these quarrelsome individuals tryptophan not only decreased quarrelsome behaviours but also increased agreeable ones. This change occurred even though, for most participants, there was no effect of tryptophan on their appraisal of the agreeableness of their interaction partners. This suggests a direct effect on behaviour, rather than an indirect effect mediated by changes in the participants' cognitive appraisal of others. In the first study the women, but not the men, did slightly better than expected by chance in guessing when they were on tryptophan and when they were on placebo. In the second study neither the women nor the men did better than expected by chance. This suggests that participants were generally unaware that their social behaviour was changed, and that the changes may have been mediated by an evolutionary old part of the brain that is not accessed by consciousness. This is consistent with the fact that altered serotonin function can influence social behaviour in organisms with very primitive nervous systems.<sup>15,16</sup> In the first study, tryptophan did not alter mood even though it influenced social behaviour. Given that the second study differed primarily in studying participants with high trait irritability, tryptophan probably had a direct effect on social behaviour in that study also. However, there was an improvement in mood that may also have fed back to potentiate the move toward more positive social behaviour.

### Effect of antidepressants on social behaviour in healthy humans

Serretti and colleagues<sup>17</sup> reviewed more than 30 studies in which the effects of antidepressants were compared with

placebo in healthy participants. They concluded that in general there were no effects on mood. Those effects that did occur were more consistent when the antidepressants were given subchronically or chronically rather than acutely, and the effects included alterations in social behaviour. Studies that found alterations in social behaviour are reviewed below.

Knutson and colleagues<sup>18</sup> gave healthy volunteers the SSRI paroxetine or placebo for 4 weeks. Paroxetine decreased subjective irritability and increased affiliative behaviour on a dyadic laboratory puzzle task. Tse and Bond<sup>19–23</sup> performed 5 studies in which the effects of antidepressants were compared with placebo when given to healthy participants. In the first study,<sup>19</sup> the SSRI citalopram and placebo were given for 4 weeks, and the outcome was the Cloninger Temperament and Character Inventory. Citalopram increased self-directedness but not cooperativeness. In the second study,<sup>20</sup> citalopram and placebo were given for 2 weeks each. Assessment was by participants' roommates and by a laboratory test involving a mixed-motive game played with a confederate. Citalopram had no effect on ratings by roommates, but increased cooperative behaviour in the laboratory game. In the third study,<sup>21</sup> participants received a single dose of placebo, citalopram or the selective noradrenaline reuptake inhibitor reboxetine. Reboxetine, but not citalopram, caused participants to show more cooperative communication with a confederate behaving in a nonsocial manner and to give more cooperative communications in a mixed-motive game. In the fourth study,<sup>22</sup> different groups were given reboxetine or placebo for 2 weeks, and the measures were the same as those in the second study. There was no effect on behaviour along the agreeable–quarrelsome dimension in the laboratory tests, but roommates considered the participants more cooperative and agreeable when receiving reboxetine. In the fifth study,<sup>23</sup> 1 member from each of 10 pairs of roommates received reboxetine and placebo for 2 weeks each in a crossover study, and the outcome measures, again, were similar. Reboxetine had no significant effect on irritability, cooperation or any other measure. Kamarck and colleagues<sup>24</sup> studied 159 individuals without axis I diagnoses who had elevated scores on 2 measures of hostility. Participants were assigned to citalopram or placebo for 2 months. Citalopram decreased ratings on self-report of state anger and hostile affect. Simmons and Allen<sup>25</sup> randomized 38 healthy people to placebo or the SSRI sertraline for an average of 23 days and administered scales assessing aspects of personality using personality inventories. Among the changes induced by sertraline were decreases in guilt and attentiveness and increases in joviality and self-assurance, but there was no change in hostility. Finally, Knorr and colleagues<sup>26</sup> examined the effect of 4 weeks of treatment with the SSRI escitalopram or placebo on personality inventory scores in 80 first-degree relatives of patients with a history of major depressive disorder. Escitalopram did not alter neuroticism, extraversion, psychoticism, openness or conscientiousness, but increased agreeableness.

The variability in the results of the studies evaluating the effects of antidepressants in healthy people is probably owing to a number of factors, including differences in study design and outcome measures as well as small sample sizes. Personality inventories are not designed to detect changes occurring

over weeks, and laboratory tests are not necessarily indicative of behaviour in everyday life. Nonetheless, several studies, including the 2 largest — those of Kamarck and colleagues<sup>24</sup> and Knorr and colleagues<sup>26</sup> — found changes consistent with improvements in behaviour along the agreeable–quarrelsome dimension. Thus, the studies provide modest support for the idea that antidepressants may decrease agonistic and increase affiliative social behaviours in humans. Among the antidepressants studied was reboxetine, a noradrenaline reuptake inhibitor. However, preclinical studies suggest that reboxetine also increases serotonin function.<sup>27</sup> Therefore, serotonin may have been a mediator of the effects of all the antidepressants.

### Effect of antidepressants on social behaviour in patients

Irritability occurs in about half of patients who are depressed, and usually resolves with successful treatment.<sup>28,29</sup> Reviews by Bond<sup>30</sup> and Painuly and colleagues<sup>31</sup> suggest that about one-third of depressed patients experience anger attacks. While irritability and anger are not often studied in relation to the treatment of depression, Fava and colleagues<sup>32</sup> compared the effects of sertraline, imipramine and placebo on anger attacks in patients with atypical depression and dysthymia. Anger attacks ceased in more than 50% of the patients in the active treatment groups compared with 37% in the placebo group.

Two studies examined aspects of personality related to affiliative behaviour in depressed patients treated with antidepressants. Agosti and McGrath<sup>33</sup> compared the effects of 10 weeks of treatment with fluoxetine, imipramine and placebo on Cloninger Temperament and Character Inventory scores. The antidepressants had no effect on cooperativeness. On the other hand, Tang and colleagues<sup>34</sup> found a significant increase in extraversion, even after controlling for depression reduction, in patients treated for 8 weeks with paroxetine relative to those treated with placebo.

A number of studies have compared the effect of antidepressants and placebo on agonistic behaviour in patients with diagnoses other than depression. Salzman and colleagues<sup>35</sup> found that fluoxetine decreased anger over 13 weeks in patients with borderline personality disorder, and Coccaro and Kavoussi<sup>36</sup> showed that fluoxetine administered for 2–3 months decreased irritability and aggression in patients with various personality disorders. However, Rinne and colleagues<sup>37</sup> found no effect of the SSRI fluvoxamine after 6 weeks of treatment on aggression in women with borderline personality disorder. Vartiainen and colleagues<sup>38</sup> treated aggressive inpatients with schizophrenia, who were on but had not responded to neuroleptics, with citalopram for 24 weeks. The drug caused a significant decrease in the frequency of aggressive incidents. McDougale and colleagues<sup>39</sup> gave fluvoxamine for 12 weeks to adults with autism and, among other changes, found a decrease in aggression.

Persistent and marked anger or irritability is a core symptom of PMDD.<sup>40</sup> Shah and colleagues<sup>41</sup> concluded from a meta-analysis that SSRIs are an effective treatment for PMDD and premenstrual syndrome (PMS). Landén and colleagues<sup>42</sup> compared short-term administration of paroxetine with placebo in the treatment of irritability in women with PMDD.

Treatment was started “in the midst of the luteal phase, when irritability had been intense for 2 days.” A significant decrease of irritability was found starting at day 3 of treatment. Kornstein and colleagues<sup>43</sup> studied patients with moderate to severe PMS who received sertraline or placebo on different schedules. Although they did not specifically study irritability, the measure of mood included irritability as well as depression and anxiety. They concluded that giving sertraline at the onset of symptoms was as effective as continuous dosing. Overall, these results support the idea that patients with elevated irritability may respond more quickly to treatment with SSRIs than patients with only depressed mood.

The results described provide substantial evidence that SSRIs can decrease aggression, anger and irritability. Whether SSRIs can increase positive social interactions in depressed patients has not been studied in placebo-controlled trials.

### Social interactions during depression and depressed mood

Hames and colleagues<sup>44</sup> reviewed the interpersonal processes thought to be involved in the initiation and maintenance of depression. Depressed patients tend to have deficits in social skills, seek reassurance excessively while also seeking negative feedback and exhibit both interpersonal inhibition and interpersonal dependency. The review does not mention that depressed patients often exhibit irritability and anger, although this topic is discussed briefly in an earlier review by Lara and Klein.<sup>45</sup> Many studies have looked at how depressed mood influences social behaviour in interaction partners. For example, Strack and Coyne<sup>46</sup> demonstrated that after euthymic individuals talked for 15 minutes to others who were dysthymic, the euthymic individuals were more hostile, anxious and depressed than those who talked to other euthymic individuals. Biglan and colleagues<sup>47</sup> studied married couples who spent 20 minutes in problem-solving discussions. In some of the couples, the wives were clinically depressed. There was a tendency for couples in which the wife was depressed to have higher rates of aggressive behaviour, and there was a strong correlation between aggression in the wives and husbands. Hokanson and Butler<sup>48</sup> studied students who were sharing dormitory rooms. Euthymic students showed higher levels of hostility toward roommates whose moods were depressed than euthymic students whose roommates showed low levels of depressed mood. In these studies there was no direct evidence that the response of others toward those with depressed moods was mediated directly by the irritability or anger associated with depression. However, as discussed in the next section, it is a plausible explanation given that quarrelsome or aggressive behaviours tend to be reciprocated by others.

### Complementarity in social interactions and its implications for mood regulation

During interpersonal encounters, people respond to the behaviours of others in a manner that is governed in part by the specific behaviour of the other. Integrating theory and research, Kiesler<sup>49</sup> proposed that a person’s interpersonal actions evoke a

complementary response that leads to a repetition of the person's original actions and that a particular level of intensity tends to evoke a response of similar intensity. Furthermore, while behaviours along the dominant–submissive dimension tend to be reciprocal, for example with dominant behaviours resulting in a submissive response, on the agreeable–quarrelsome dimension there is correspondence, with agreeableness producing an agreeable response and quarrelsomeness producing a quarrelsome response. Many studies<sup>50–56</sup> support the idea that quarrelsomeness tends to evoke quarrelsomeness and agreeableness tends to evoke agreeableness, although the exact response can be modulated by the context. Moskowitz and Côté<sup>57</sup> used an ecological momentary assessment method to study behaviour along the agreeable–quarrelsome dimension and mood during individual social interactions. Most individuals experienced positive affect when they were agreeable during interactions, and negative affect when they were quarrelsome. In those with high trait quarrelsomeness the associations with affect were reversed and they experienced positive affect during quarrelsome interactions. However, the association between positive behaviour and positive mood in most people was confirmed by Côté and Moskowitz.<sup>58</sup> They also found that individuals with elevated neuroticism were less likely to engage in agreeable behaviours and experienced less pleasant affect than others when they were agreeable. Taken together, these studies suggest that in most people more agreeable behaviours toward others will tend to be reciprocated and will result in a more positive mood. Similarly, more quarrelsome behaviours will tend to be reciprocated, and will result in a more negative mood.

In everyday life, complementarity of agreeable and quarrelsome behaviours, together with changes in mood and appraisal of others, may contribute to an iterative cycle. Recent results by Sadikaj and colleagues<sup>59</sup> suggest a cycle in which perceiving an interaction partner as quarrelsome can lead to negative affect and subsequent quarrelsome behaviour, which would presumably elicit the same sequence in the interaction partner, resulting in complementarity of the quarrelsome behaviour and thereby renewing the cycle. An intervention that decreases quarrelsome behaviours and increases agreeable behaviours would help to break the cycle, leading to improved mood.

### **Possible role of changes in social behaviour along the agreeable–quarrelsome dimension in the effects of antidepressants on mood**

The research mentioned previously suggests (i) most antidepressants enhance serotonin function; (ii) serotonin influences behaviour along an agreeable–quarrelsome dimension; (iii) patients who are depressed tend to be irritable and sometimes have anger attacks; (iv) people tend to respond to irritable or quarrelsome behaviour with quarrelsome behaviour, and they respond to agreeable behaviour with agreeable behaviour; and (v) more quarrelsome interactions tend to be associated with more negative mood, and more agreeable behaviour tends to be associated with more positive mood. The tendency of antidepressants and increased serotonin to decrease quarrelsome or agonistic behaviour and to increase agreeable or affiliative behaviour might be expected to improve mood. Thus, our hy-

pothesis is that changes in social behaviour are a way in which antidepressants can improve mood. The change in mood after each social interaction will be small, but after many interactions over a period of days or weeks, especially when they involve the same person, the effect should be much greater. This idea is consistent with the slow onset of action of antidepressants.

Increases in positive affect associated with more positive social interactions and decreases in negative affect associated with fewer negative social interactions may both play a role in the improvement in mood in depressed patients. However, in depressed patients, increases in positive affect may be more important than decreases in negative affect. Although positive and negative affect tend to be moderately negatively correlated, research by Watson and Clark<sup>60</sup> and by Crawford and Henry<sup>61</sup> suggests that they are separate dimensions rather than opposite sides of a continuum. A systematic review by van der Rot and colleagues<sup>62</sup> examined ecological momentary assessment studies conducted in patients with depression. As expected, symptomatic patients displayed less positive affect and more negative affect than controls. However, surprisingly, when they experienced a positive event, they reported more positive affect and less negative affect than controls. Geschwind and colleagues<sup>63</sup> found that “early improvement in positive rather than negative emotion predicted remission from depression after pharmacotherapy.” Wichers and colleagues<sup>64</sup> studied patients receiving a combination of psychotherapy and antidepressants and found that in those who responded to treatment relative to those who did not respond to treatment boosts in positive affect were followed by a stronger suppression of negative affect over the next few hours. These results suggest that the enhancement of positive social behaviour may be more primary in the action of antidepressants than the inhibition of negative social behaviour.

### **Role of more prosocial behaviour and other mechanisms in mediating the response to antidepressants**

A biological theory of the slow onset of antidepressant drugs is that they initially inhibit the firing of serotonergic neurons, yet adaptive changes occurring over a few weeks result in important increases in serotonin function.<sup>1</sup> Nonetheless, in rats there is a small increase in extracellular serotonin after a single dose of an SSRI.<sup>65</sup> Similarly, in rats acute doses of tryptophan decrease the firing rate of serotonin neurons, but nonetheless can cause small increases in serotonin release.<sup>66</sup> The effect of tryptophan on human social behaviour was similar during successive 3-day periods across 2 weeks of administration,<sup>13,14</sup> suggesting that small increases in serotonin release may be enough to promote more positive social interactions. This does not rule out the possibility that the larger increases in serotonin that occur later during antidepressant treatment can have a direct effect on mood. A temporary reversal of the antidepressant effect of SSRIs can be achieved within a few hours using tryptophan depletion.<sup>67</sup> Given the rapidity of this effect it is likely to be a direct effect on mood. The improvement in mood mediated by changes in social behaviour may be important in the initial effects of antidepressants, but may be augmented by direct effects on mood associated with larger increases in serotonin function occurring at later times.



The cognitive neuropsychological model of antidepressant action put forward by Harmer and colleagues<sup>2,68</sup> suggests that from initiation of treatment antidepressants create implicit positive biases in attention, appraisal and memory and that the delay in effects on mood are due to the time that it takes for these emotional processing biases to influence mood. The model is based on evidence that, for example, acute or sub-chronic administration of antidepressants will counter the tendency of depressed patients to classify ambiguous facial expressions as negative, increase recognition of happy facial expressions and improve recall of positive adjectives in a memory task. The cognitive neuropsychological model has similarities to, and important differences from, the social interaction model proposed here. Both models suggest that antidepressants alter responses to stimuli. In the cognitive neuropsychological model the change is to a more positive appraisal of neutral and emotional stimuli. In the social interaction model the stimuli are people whom a depressed patient encounters in daily life, and the change is a shift away from quarrelsome and toward more agreeable behaviour. The important difference is in how the altered response to a stimulus improves mood. In the cognitive neuropsychological model the changes occur purely in the mind, with more positive appraisals of stimuli progressively improving mood. In the social interaction model the change is in behaviour, specifically how agreeable and quarrelsome the person is toward others. The mood improvement follows from more positive social interactions resulting from the decrease in quarrelsomeness and increase in agreeableness of the depressed person and the corresponding changes that result in the interaction partners. Although the 2 theories differ in important ways, they are not mutually exclusive, and both could be operating. Thus, antidepressants may be moving behaviour from quarrelsome to agreeable while at the same time reinforcing this change through more positive cognitive appraisal of memories and situations, which would include more positive appraisal of interaction partners. The more positive responses of interaction partners would initiate a cycle of more positive social behaviour, and this iterative process would result in a clinically significant improvement in mood.

## Conclusion

This commentary proposes that one mechanism of antidepressant drugs is that they promote more positive social interactions. Currently the evidence is stronger for increased serotonin function and antidepressants decreasing aggressive and irritable behaviour than for them increasing agreeable behaviour. In particular there is some inconsistency in the results on the effects of antidepressants on agreeable behaviour, but this is possibly owing in part to the use of measures that were not entirely appropriate for the measurement of agreeableness. Furthermore, much of the evidence for more agreeable social behaviour is based primarily on studies with healthy people rather than depressed patients. Further research is needed on depressed patients using suitable measures of both quarrelsomeness and agreeableness, such as the ecological momentary assessment method described earlier.

Our theory is compatible with others. Future studies using ecological momentary assessment during the first few weeks of antidepressant treatment may provide evidence consistent with our social interaction model. However, determining cause and effect may be difficult. Thus, changes in mood may occur in parallel with changes in cognitive appraisal and changes in social behaviour. Also, changes in cognitive appraisal and social behaviour may interact to alter mood. For example, a depressed patient being treated with an antidepressant may appraise others in a more positive light, which could contribute to more positive social behaviour. Furthermore, a less quarrelsome and more agreeable social interaction may be appraised as a more positive experience, thereby enhancing its effect on mood. Nonetheless, the social interaction model leads to a potentially testable outcome. Social isolation contributes to the onset of depression and is commonly seen in depressed patients.<sup>44</sup> A more limited number of social interactions will limit the potential for more positive social interactions to improve mood. If more positive social interactions are a clinically significant factor in the action of antidepressants, then patients who have a greater number of social interactions during the early stages of treatment with antidepressants might be expected to respond better to treatment.

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