Reboxetine Promotes Social Bonding in Healthy Volunteers

Wai S. Tse and Alyson J. Bond

J Psychopharmacol 2003 17: 189
DOI: 10.1177/0269881103017002007

The online version of this article can be found at:
http://jop.sagepub.com/content/17/2/189
Reboxetine is a novel antidepressant with a selective action on noradrenaline. In addition to its efficacy in depression, it has been found to improve social adaptation. The objective of this study was to assess the specific social behavioural effects of reboxetine which might be associated with social adaptation. Ten pairs of healthy volunteers took part in a randomized double-blind, crossover study of 2 weeks treatment with reboxetine (4 mg b.d.) and placebo with a 2-week washout period. In each pair, one person (subject) took the tablets and the other (flatmate) received no treatment. On the last day of each treatment period, the subjects socially interacted with a stranger (a confederate behaving as a responsive person) in a stranger–dyadic social interaction paradigm. After the interaction, subjects played the Mixed-Motive game, which measures cooperative behaviour and communication, with the confederate. Subjects read a short story before and after the social interaction. The flatmates evaluated the social behaviour of the subjects before and at the end of the two treatment periods. On reboxetine, the subjects were rated to be significantly more agreeable and cooperative (passive participant) and less submissive by their flatmates. They showed significantly less eye contact with the confederate in the social interaction paradigm and gave significantly fewer helplessness messages during the game. They spoke faster on the reading task after the social interaction. This study provides evidence that reboxetine increases cooperative social behaviour and increases social drive, which might be important for social adaptation.

Key words: cooperation, noradrenaline, social behaviour, social drive

Introduction

Reboxetine is a novel antidepressant which inhibits the reuptake of noradrenaline more specifically than previous drugs. It has been shown to be as effective in treating depression as fluoxetine, a selective serotonin reuptake inhibitor (SSRI) and to have superior efficacy in patients with severe depression (Massana, 1998). However, in addition to its efficacy in alleviating symptoms of depression, reboxetine has also been found to be more effective than fluoxetine in improving the social adaptation of depressed patients (Dubini et al., 1997). This improvement in social adaptation is thought to be associated with the treatment itself and independent of symptom resolution (Weissman, 1997).

Treatment with antidepressants has been found to improve many aspects of human social behaviour (e.g. speech, eye contact, communication) (Weissman, 2000). Fossi et al. (1984) showed that 4 weeks of treatment with a tricyclic antidepressant increased both eye contact and verbal communication in depressed patients. Antidepressant treatment can also affect speech tone and expression. In a novel approach, Stassen et al. (1998) found that changes in speech characteristics were an early sign of antidepressant-induced improvement in depressive symptoms. Interestingly, these effects of antidepressants are not confined to patients with depression. Improvements in eye contact were observed in adults with pervasive development disorders after treatment with clomipramine (Brodkin et al., 1997) and changes in speech fluency were observed in non-depressed people with stutters after treatment with clomipramine or desipramine (Stager et al., 1995). Such changes are therefore unlikely to be due solely to depressive symptom resolution and might be a direct result of neurotransmitter action.

Work studying the actions of neurotransmitters in humans is limited by the drugs available. Reboxetine is the first of a new class of antidepressant drugs with relative specificity for the noradrenergic system. In comparison, previous drugs with noradrenergic actions had numerous additional non-specific effects on other neurotransmitters. The evidence to support the specific involvement of noradrenaline in human social behaviours came from clinical studies and the finding that reboxetine improved the social functioning of depressed patients more than fluoxetine should stimulate experimental studies to investigate this effect in more detail. One study has compared the effects of a single dose of reboxetine (4 mg), citalopram (10 mg) and placebo on cooperative social behaviour in a stranger–dyadic social interaction procedure in healthy volunteers (Tse and Bond, 2002a). Reboxetine was found to increase cooperation in the game situation, in which the volunteers both communicated and played more cooperatively with a drug-free partner. Citalopram...
was not significantly different from placebo on these measures.

Although, the acute administration of reboxetine led to more cooperative social behaviour in a stranger–dyadic social interaction procedure, longer-term administration of antidepressants might have different effects on social behaviour. Clinical effects of antidepressants can be observed in the first 2 weeks (Stassen et al., 1998) and of reboxetine as early as day 10 (Versiani et al., 2000). Recent experimental studies of serotonergic antidepressants demonstrated that they can enhance some aspects of social behaviour. For example, Knuston et al. (1998) showed that 1 week of administration of paroxetine to healthy volunteers increased their affiliative behaviour with a stranger during a tangrams game. Similarly, Tse and Bond (2002b) reported that healthy volunteers receiving 2 weeks of citalopram treatment showed more cooperative game behaviour during the Mixed-Motive game. Therefore, a study of 2 weeks of administration of clinical doses of reboxetine to healthy volunteers could lead to more understanding of the behavioural effects of noradrenaline instrumental in the improvement found on social adaptation in clinical studies.

Social functioning describes an individual’s interactions with people in different contexts. There are differences between social interaction patterns with a stranger and with a friend (Fehr, 1996), and antidepressants might have distinct effects on these. For example, Tse and Bond (2002b) showed that healthy volunteers receiving 2 weeks of citalopram became more assertive with their flatmates, but were more dominant and cooperative with a stranger. Most people with psychological problems initially confide in someone with whom they have a close relationship. Only a small percentage of them go on to seek professional help. The social effects of reboxetine observed from interactions with close friends thus might be relevant to the clinical effects on social functioning, as well as interactions observed with a stranger in an experimental setting or self-reported social adaptation.

The aim of the present study was to explore the role of noradrenaline on the social behaviour of healthy volunteers when they were interacting with an unfamiliar person, a stranger, and with a familiar person, their flatmate, by using reboxetine. Reboxetine is a novel selective noradrenaline reuptake inhibitor with minimal effects on other neurotransmitter systems (Dostert et al., 1997). The relative specificity of action of reboxetine therefore, makes it a powerful tool with which to investigate noradrenergic effects on social behaviour (Wong et al., 2000).

Materials and methods

Subjects

Ten pairs of same-sex healthy volunteer flatmates (six male pairs and four female pairs) were recruited for the experiment. Exclusion criteria were current or previous history of psychiatric illness, current physical illness, or use of any medication or recreational drugs during the last month. Subjects were asked to refrain from alcohol during the trial period. All volunteers gave their written informed consent and the study was approved by the institutional ethical committee.

Design and drugs

A randomized, double-blind, placebo-controlled crossover trial of reboxetine versus placebo was conducted. In each of the 10 pairs of volunteers, one (subject) volunteered to take the tablets and the other (flatmate) received no treatment. Reboxetine (4 mg b.d.) and placebo were administered orally as identical capsules for 2 weeks. The subjects were randomly assigned to receive either reboxetine or placebo first and there was a 2-week washout period following the first treatment.

Rating scales

Depression and anxiety were assessed with the Beck Depression Inventory (BDI) (Beck et al., 1988) and the trait version of the State Trait Anxiety Inventory (STAI) (Spielberger et al., 1970). The Positive and Negative Affect Scale (PANAS) (Watson et al., 1988) was used to measure two dimensions of current affect: positive and negative. Each dimension contains 10 items rated on a scale of 1–5. The Social Adaptation Self-evaluation Scale (SASS) (Bosc et al., 1997) was used to assess levels of social functioning. There are 21 items and the scores range from 20 to 60. Drug side-effects were measured by a 9-item Bodily Symptom Scale (BSS). Subjects were asked to rate dryness of mouth, anxiety, sweating, palpitations, nausea, dizziness, irritability, physical tiredness and concentration on 100-mm visual analogue scales between absent and severe. The Post Encounter Scale (PES) (Coyne, 1976) is a 7-item self-report inventory to assess the level of rejection of a particular person. Each item is rated on a scale of 1–6. The Communication Checklist (Hokanson et al., 1980) is a computerized 24-item inventory to allow dyads to communicate during the Mixed-Motive game. The checklist measures six different types of communication: extrapunitiveness; cooperativeness/friendliness; ingratiation; sadness/self-devaluation; blaming partner/devalued feeling; helplessness/withdrawal. Each item is rated on a scale of 0–4. The Impact Message Inventory (IMI) (Kiesler et al., 1985) is a 90-item self-report inventory to assess eight different types of covert reactions towards a specified person (flatmate) evoked during interpersonal transactions: dominant, friendly dominant, friendly, friendly submissive, submissive, hostile–submissive, hostile, hostile–dominant. The Two Dimension Social Interaction Scale (2DSIS) (Tse and Bond, 2001) is a 28-item observer rating scale to assess four different categories of social behaviour: active participant, active nonparticipant, passive participant and passive nonparticipant. Each item is rated on a scale of 1–7.

The Mixed-Motive game

This is a modified version of the Prisoner’s Dilemma game (Hokanson et al., 1980) which was played on a computer. There are 30 trials in the game which are divided into two sections. Between each section, subjects are required to fill in the communication checklist to send to their partner. They then receive one from their partner. Each trial involves selecting a particular scheme of pay-off. Each pay-off scheme indicates how points are being distributed to each of the two players. This selection is based on two sequential choices by the two players. The first choice is decided by one player (confederate). The player has a choice of three sets of pay-off schemes from which to choose a particular set. In the current experiment, the choice of the confederate was predetermined such that the three schemes were selected evenly over the whole game. The second choice is decided by the other player (subject) who selects one option from the set chosen by the first player. In this selection procedure, the second person has a higher
power to determine how many marks to distribute to the first person. The subjects were therefore able to give the confederate more points (injuring), the same points (cooperative) or lower points (punitive) than themselves.

**Voice recording and speech analysis**

Three different simple short stories consisting of 60 words and lasting approximately 30 s were read by the volunteers. All story readings were carried out in an acoustically shielded room and digitally recorded on a computer with a sampling interval of 60 × 10⁻⁶ s. Speech analysis was based on a study conducted by Stassen et al. (1998). The acoustic variables included: (i) total pause duration: only pauses ≥ 250 ms were included; (ii) total duration of speech including pauses; (iii) duration of active speech without pauses; (iv) mean energy per second; and (v) variation of energy per second.

**Dyadic interaction and social behaviour variables measured**

The confederates were two females and two males recruited from a university drama department. They were blind to the experimental hypothesis and were trained for 6 h to play one role based on a study conducted by Sacks and Bugental (1987). This role represented a quiet but responsive person. The confederates were instructed to respond to the subject’s conversation slowly with relevant topics. They smiled and engaged in eye contact during conversation. They spoke little and rarely initiated conversation but the topics were relevant to the subjects. Five behavioural variables were chosen for measurement: total duration of speech (SPEECH); proportion of subject’s speech with eye contact (GAZE); proportion of subject’s speech with no eye contact (NOGAZE); proportion of confederate’s speech with eye contact from subject (LOOK); and proportion confederate’s speech with no eye contact from subject (NOLOOK). The absolute amount of these social behaviours might be strongly affected by the role of the confederate and so proportions such as GAZE, NOGAZE, LOOK, and NOLOOK were used to produce a better inference of the treatment effects.

GAZE was calculated by measuring the total duration of eye contact while the subject was speaking divided by the total duration of speech (SPEECH). NOGAZE was calculated by summing the duration of each sentence spoken by the subject during which the subject showed no eye contact at all divided by the total duration of speech (SPEECH). LOOK was calculated by measuring the total duration of eye contact while the confederate was speaking divided by the total duration of speech by the confederate. NOLOOK was calculated by summing the duration of each sentence spoken by the confederate during which the subject showed no eye contact at all divided by the total duration of speech by the confederate.

**Procedure**

At the baseline of each treatment phase, subjects completed the BDI, STAI, PANAS, BSS and SASS and then they were asked to read a passage aloud while their voice was recorded. Flatmates were asked to complete the IMI and 2DSIS based on their impression of the subject in the last 2 weeks. On the test day of each treatment phase (day 14 of each treatment period), subjects and flatmates completed the same questionnaires as at baseline and the subjects were also asked to read a passage aloud while their voice was recorded. The subjects were then led to a waiting room, equipped with a hidden camera where the sex matched confederate was sitting. As soon as the subject entered the waiting room, video recording started and was taken for 3 min. Immediately following this, subjects were led to a game room equipped with a computer. They filled in the PES and their voice was recorded. They were then given instructions for the mixed-motive game, which they were told they would be playing by computer with the volunteer (confederate), whom they had just met. The responses of the confederate were pre-programmed into the computer so that they were standard for all subjects. At the end of the study, all subjects were debriefed and their permission to use the video recording was sought. All subjects gave written permission. The video recordings were analysed by a graduate psychologist and an experienced observer who were blind to drug treatment. The graduate psychologist measured the duration of the selected social behaviours for each subject. The observer rated the subject’s social interaction by using the 2DSIS.

**Statistical analysis**

The results were analysed using SPSS 10.0 (SPSS Inc., Chicago IL, USA). To examine the effect of reboxetine on variables measured both at baseline and after treatment such as depression and anxiety scores, the two baseline measures at the beginning of each treatment period were used as covariates and analysis of covariance (ANCOVA) for crossover trials was performed as recommended by Senn (1993). Social behaviour was only measured during the two treatment phases and so the effects of reboxetine on social behaviour in the stranger–dyadic social interaction paradigm were analysed according to the recommendations by Hills and Armitage (1979) to minimize period effects. However, the reactions of the subjects towards the confederate might also influence social behaviour in the interaction and PES scores were used as a covariate in this analysis. To examine drug effects on acoustic variables, two separate ANCOVAs were performed for speech before and after the social interaction. For the acoustic variables on the test day (before the social interaction), the baseline measures at the beginning of each treatment period were used as covariates. For those after the social interaction, the measures just before the social interaction were chosen as covariates. The estimate marginal (EM) means during placebo and reboxetine treatment are reported.

**Results**

There were no differences at baseline in age or scores on the BDI, STAI, SASS and PANAS between those who started with reboxetine and those who started with placebo. The means for the overall group are shown in Table 1. The SD for the BDI was observed to be high and so the individual scores were checked and the high SD was found to be due to one outlier with a BDI of 28. The mean BDI excluding this subject was 3.56 (2.19). The subject was included in the analysis because the baseline BDI in the second phase of treatment was 14 after receiving placebo treatment in the first treatment phase. There were no significant differences between reboxetine and placebo treatment on positive or negative mood, or social adaptation (Table 2). There were no significant
differences between reboxetine and placebo treatment on bodily symptoms.

**Impact message inventory**
A significant difference on the dimension of submissiveness was found between the treatments ($t_{7} = –2.43$, SE = 1.82, $p < 0.05$). The result showed that flatmates reported the subjects to be significantly less submissive when they were taking reboxetine than placebo (EM means for placebo = 10.85 and reboxetine = 8.60). However, the subjects did not report any significant difference between treatments in how they were interacting with their flatmate.

Mixed-Motive game and communication checklist
There were no significant differences in the player scores on the game between the two treatments (Table 3). However, on the communication checklist, a significant difference between treatments was found on the dimension of helplessness ($t_{7} = –4.00$, SE = 0.76, $p < 0.05$). When the subjects were taking reboxetine, they sent significantly fewer helplessness messages than when they were taking placebo. There were no significant differences on the PES between the two treatments (EM means for placebo = 22.18 and reboxetine = 22.60).

Social behaviour during the stranger–dyadic social interaction
The EM means for the five social behaviours are shown in Table 4. A significant treatment effect was found on LOOK ($t_{7} = –3.27$, SE = 0.09, $p < 0.05$). Reboxetine significantly reduced eye contact when the confederate was speaking.

---

**Table 1** Mean ± SD questionnaire scores of volunteers on the first day of the experiment

<table>
<thead>
<tr>
<th></th>
<th>Mean ± SD (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>20.9 ± 1.52</td>
</tr>
<tr>
<td>State Trait Anxiety Inventory: total score</td>
<td>38.6 ± 10.42</td>
</tr>
<tr>
<td>Beck Depression Inventory: total score</td>
<td>6.00 ± 8.00</td>
</tr>
<tr>
<td>Social Adaptation Self-evaluation Scale</td>
<td>42.40 ± 5.32</td>
</tr>
<tr>
<td>Positive and Negative Affect Scale</td>
<td></td>
</tr>
<tr>
<td>Positive subscale</td>
<td>33.20 ± 6.43</td>
</tr>
<tr>
<td>Negative subscale</td>
<td>17.80 ± 7.53</td>
</tr>
</tbody>
</table>

**Flatmates' rating of 2DSIS**
A significant treatment effect was found ($t_{7} = 3.51$, SE = 1.71, $p < 0.01$). Subjects were rated significantly higher in the category of passive participant by their flatmates (EM means for placebo = 19.28 and reboxetine = 22.28).

**Table 2** Estimated marginal mean ± SE questionnaire scores of volunteers for the two treatment phases

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 10)</th>
<th>Reboxetine (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>State Trait Anxiety Inventory: total score</td>
<td>34.30 ± 3.70</td>
<td>32.90 ± 3.16</td>
</tr>
<tr>
<td>Beck Depression Inventory: total score</td>
<td>5.68 ± 4.15</td>
<td>1.62 ± 3.42</td>
</tr>
<tr>
<td>Social Adaptation Self-evaluation Scale</td>
<td>43.1 ± 2.12</td>
<td>43.80 ± 2.00</td>
</tr>
<tr>
<td>Positive and Negative Affect Scale</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive subscale</td>
<td>29.67 ± 2.87</td>
<td>31.83 ± 3.03</td>
</tr>
<tr>
<td>Negative subscale</td>
<td>16.98 ± 3.09</td>
<td>14.82 ± 2.87</td>
</tr>
</tbody>
</table>

**Table 3** Estimated marginal mean ± SE scores awarded by the participants on the Mixed-Motive game and on the communication checklist for the two treatment phases

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 10)</th>
<th>Reboxetine (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mixed-Motive game</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Participant’s score</td>
<td>70.71 ± 2.88</td>
<td>69.00 ± 2.99</td>
</tr>
<tr>
<td>Confederator’s score</td>
<td>85.12 ± 15.78</td>
<td>84.09 ± 16.40</td>
</tr>
<tr>
<td>Communication checklist scores</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extrapunitive</td>
<td>0.90 ± 0.35</td>
<td>0.90 ± 0.37</td>
</tr>
<tr>
<td>Cooperative</td>
<td>10.27 ± 1.27</td>
<td>9.18 ± 1.32</td>
</tr>
<tr>
<td>Ingratiation</td>
<td>6.17 ± 0.75</td>
<td>5.19 ± 0.78</td>
</tr>
<tr>
<td>Sadness</td>
<td>1.80 ± 0.56</td>
<td>1.40 ± 0.58</td>
</tr>
<tr>
<td>Blaming</td>
<td>2.13 ± 0.70</td>
<td>2.30 ± 0.73</td>
</tr>
<tr>
<td>Helplessness</td>
<td>4.44 ± 0.40</td>
<td>2.91 ± 0.41*</td>
</tr>
</tbody>
</table>

*Significant difference between reboxetine and placebo treatment ($p < 0.05$).

**Table 4** Estimated marginal means ± SE for the five social behaviours in the participants during the stranger–dyadic social interaction in the two treatment phases

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 10)</th>
<th>Reboxetine (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GAZE</td>
<td>0.37 ± 0.02</td>
<td>0.34 ± 0.03</td>
</tr>
<tr>
<td>NOGaze</td>
<td>0.14 ± 0.05</td>
<td>0.12 ± 0.05</td>
</tr>
<tr>
<td>LOOK</td>
<td>0.78 ± 0.05</td>
<td>0.64 ± 0.05*</td>
</tr>
<tr>
<td>NOLOOK</td>
<td>0.10 ± 0.03</td>
<td>0.08 ± 0.03</td>
</tr>
<tr>
<td>SPEECH</td>
<td>83.05 ± 9.32</td>
<td>96.45 ± 9.70</td>
</tr>
</tbody>
</table>

*Significant difference between the reboxetine and placebo treatment ($p < 0.05$).
A significant treatment effect was found on the observer rating on the 2DSIS ($t_7 = 2.73$, $SE = 3.75$, $p < 0.05$). Subjects were rated as significantly higher in the category of passive nonparticipant during the social interaction (EM means for placebo = 14.40 and reboxetine = 19.50).

**Speech analysis**

ANOVA found there were no treatment effects on any acoustic variables after 2 weeks of treatment before the social interaction. However, a significant treatment effect on total duration of speech after the social interaction was found ($t_7 = –3.12$, $SE = 0.33$, $p = 0.015$). The result showed that total duration of speech after reboxetine treatment was significantly reduced compared to placebo (EM means for placebo = 16.24 and reboxetine = 15.71).

**Discussion**

This study is novel in examining the social behavioural effects of a 2-week course of treatment with reboxetine on healthy volunteers in different kinds of interaction: first, with a familiar person (a flatmate), second, with a stranger and, third, on a scale of self-assessment of social functioning specifically designed to measures general social adaptation in society. Flatmates, who received no treatment, reported that the subjects behaved in a more passive participant manner (2DSIS) and showed decreased submissiveness (IMI) when taking reboxetine compared to placebo. The items which load on the passive participant scales of the 2DSIS are cooperative, agreeable, attentive and considerate. The flatmate therefore perceived the subjects to have more of these characteristics when they were taking reboxetine. The increase in rating of these traits might indicate that the subjects were more concerned about their flatmates, made more effort to fit into their lives and were motivated to maintain a good relationship with them. One of the possible results from the increase in cooperation might be a reduction of conflict. Legge and Rawlins (1992) found that cooperation helps dispute management in adults. Skill in managing potential sources of conflict between friends is important for the maintenance of friendship. Therefore, when the subjects were taking reboxetine, the increased cooperation and attentiveness noted by the flatmates might have reduced any potential conflicts and promoted friendship building. These effects are in line with the suggestion by Tse and Bond (2002a) that ‘repeated doses (of reboxetine) might promote social bonding leading to better social adaptation’.

The flatmates also rated the subjects as showing a decrease in submissive behaviour on the IMI after 2 weeks of reboxetine treatment. However, they did not rate any increase in dominance or hostility. This reduction of submissiveness towards the flatmates might represent a sign of increased assertiveness or independence. On the IMI, the items associated with the concept of submissiveness are, for example: ‘When I am with this person he makes me feel in charge’; ‘When I am with this person he makes me feel that I should tell him to stand up for himself’; and ‘When I am with this person it appears to me that he sees me as superior’. When the flatmates reported that the subjects aroused fewer of these kinds of feelings in them, the decrease in submissiveness could be interpreted as an increase of assertive behaviour leading to more respect and a more equal partnership. These results together suggested that reboxetine might promote social bond formation. Wilkinson and Canter (1982) suggested that assertive behaviour includes: (i) coping with refusal; (ii) standing up for your rights; (iii) making a request; and (iv) refusing a request. These behaviours could help the subjects to engage in less involuntary submissive behaviours. Allan and Gilbert (1997) suggested that involuntary submissiveness, including complying with requests of others when one does not want to, puts a cost on the one who performs such behaviour. The effects of reboxetine on submissiveness may therefore reduce the cost to the subjects of maintaining and developing the existing relationship. However, the results on the IMI should be interpreted cautiously. Only one of the eight subscales showed effects and as the scales are intercorrelated, the acceptable significance value should probably be decreased accordingly. This result in the present study is therefore tentative and needs to be replicated.

In the stranger–dyadic social interaction, reboxetine treatment reduced the amount of eye contact the subjects made with a stranger (confederate) while the stranger was speaking, compared to placebo. This behaviour suggests that the subjects were trying to avoid social contact with the stranger and in confirmation of this, they were also rated to be more passive nonparticipant during the interaction by an observer on the 2DSIS. This scale category includes adjectives such as detached, reserved and undemanding. Allan and Gilbert (1997) suggested that these behaviours are indicative of submissiveness. Although different in quality, this behaviour might be consistent with the cooperative social behaviour displayed by the subjects to their flatmates. The subjects might be trying to avoid direct conflict with strangers by showing more submissive behaviour, so that they would be more acceptable to them. This could be one of the strategies used by the subjects, when on reboxetine, to deal with an interaction with an unfamiliar person. After the brief interaction, the subjects played the mixed motive game with the confederate. There was no difference between treatment conditions in the number of points they awarded the confederate but they reported less helplessness (e.g. ‘I feel like giving up on this’; ‘most people make me discouraged’) on the communication checklist during the game, after reboxetine compared to placebo. The reduction in messages of helplessness could be another sign of increased assertion which is believed to be important for cultivating the development of relationships in the long term. It should be pointed out that the subjects in this study were already very cooperative as judged by their scores on the Mixed-Motive game. They awarded the confederate more points than themselves and their scores on cooperativeness were near the maximum possible on both occasions. There was therefore little room for improvement. In order to display prosocial drug effects on these measures, it may be necessary to have subjects who behave less cooperatively on this task, as in our previous studies (Tse and Bond, 2000a,b).

Dubini et al. (1997) found that reboxetine treated depressed patients reported higher social adaptation scores than those treated with fluoxetine. In the current study, the subjects’ scores on the SASS did not change. This was probably because they had high levels of social functioning at the start of the study, allowing little room for improvement. Their mean score of 42.4 was similar to norms for healthy subjects (Bosc et al., 1997) and for depressed patients in remission (Dubini et al., 1997).
Noradrenaline has been claimed to improve drive or motivation and studies with reboxetine provide some evidence in confirmation. Reboxetine has not been found to impair psychomotor or cognitive functions in single dose (Kerr et al., 1996; Hindmarch, 1997) or repeated dose studies (Siepmann et al., 2001). It has been found to decrease anxiety without producing sedation (Phillips et al., 2000) and even to have some alerting effects measured by pharmaco-encephalography (Herrmann and Fuder, 1998) and temporal information processing (Rammayer et al., 2001). The alerting actions of reboxetine may contribute to its positive effects on social motivation (Healy and McMonagle, 1997). However, supporting behavioural evidence for such improvement has not been available until now. In the present study, a decrease of speech duration (increase in speech rate) in the story reading after the stranger–dyadic social interaction was found after reboxetine compared to placebo. However, speech duration did not show any significant change when measured before the social interaction. The results show that social interaction with a stranger induced changes in speech characteristics only when the subjects were treated with reboxetine. While on reboxetine, the subjects read faster after the social interaction than before the social interaction. This improvement in speech fluency may be indicative of reboxetine’s effect on drive or energy, which became evident only after an experimental social interaction. The increase in speech rate could therefore be an additional indicator of enhancement of social motivation, given suitable circumstances.

Reboxetine therefore resulted in different effects in different interactions. Flatmates reported more cooperation and attentiveness from the subject while on reboxetine treatment. However, a different pattern of behaviour was detected with a stranger. The subject behaved more submissively during the interaction although they sent few messages of helplessness on the subsequent game and showed more verbal fluency after the interaction. In a recent similar study with an SSRI (Tse and Bond, 2002b), 2 weeks of treatment with citalopram also exerted different effects in the two interactions but the two drugs showed a different profile of effects. In both studies, the antidepressants decreased submissiveness rated by the flatmate and so this may be a general effect where actions of antidepressants acting principally on different neurotransmitters overlap and promote assertiveness or self-efficacy. However, flatmates did not rate increased cooperation from the subject after citalopram. In the stranger interaction, healthy volunteers showed a dominant pattern of eye gaze with a stranger after citalopram which was followed by increased cooperativeness on the subsequent game but no effects on speech fluency. The distinct behavioural effects of these two different kinds of antidepressants might relate to their neurochemistry. Drugs which act principally on noradrenaline might be more likely to promote social bonding within the subject’s social circle as well as enhancing energy, leading to more contact with friends and increased social adaptation. Drugs acting principally on serotonin might enhance social status and affiliative behaviour with strangers which might lead to prosocial effects, particularly decreasing irritability and aggression. However, these effects may be defined by the particular situations studied. More work using novel techniques to explore putative actions of antidepressants is necessary to isolate distinct effects so that treatment may be targeted to the individuals who will benefit most.

Social Anxiety Disorder (SAD) is a condition in which social functioning is profoundly impaired (Stein and Kean, 2000). People diagnosed with SAD experience severe anxiety when mixing with other people which results in underachievement in several areas of life. The whole social network at home, at work and during leisure time is affected. The current study has shown that reboxetine can exert effects on the social behaviour of healthy, well-functioning adults with both a friend and a stranger. It therefore seems likely that reboxetine would have beneficial effects in SAD. The effects on social bonding might improve interactions within the immediate circle of family and close friends. Increased energy or drive might enable patients to participate more in leisure activities and improved self-efficacy might help performance in new social situations. Specific hypotheses could be tested in a clinical study.

The present study shows that noradrenaline has a role in modulating human social behaviour. Previous work implicating a role for noradrenaline in human social behaviour has been based on the use of the SASS in clinical studies with reboxetine (Dubini et al., 1997) but, unsurprisingly, the SASS has not proved to be sensitive to drug effects in healthy volunteers and there is little experimental work in humans or animals. The introduction of reboxetine as a relatively selective noradrenaline reuptake inhibitor could help to clarify the role of noradrenaline on many kinds of social behaviour. It has been suggested that the psychosocial functioning of patients is important in the therapeutic process (Healy and McMonagle, 1997). Thus, it is important to elucidate the role of noradrenaline on human social behaviour and motivation and the study of specific behaviours requires more attention in the future.

Acknowledgement

This work was carried out while A.J.B. held a programme grant from the MRC (UK) and the study was totally funded from this source.

Address for correspondence

Alyson Bond
PO48
National Addiction Centre
Institute of Psychiatry
London SE5 8AF
UK
Email: a.bond@iop.kcl.ac.uk

References


