Tramadol and another atypical opioid meperidine have exaggerated serotonin syndrome behavioural effects, but decreased analgesic effects, in genetically deficient serotonin transporter (SERT) mice

Meredith A. Fox, Catherine L. Jensen and Dennis L. Murphy
Laboratory of Clinical Science, National Institute of Mental Health, National Institutes of Health, Bethesda MD, USA

Abstract
The serotonin syndrome is a potential side-effect of serotonin-enhancing drugs, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs) and monoamine oxidase inhibitors (MAOIs). We recently reported a genetic mouse model for the serotonin syndrome, as serotonin transporter (SERT)-deficient mice have exaggerated serotonin syndrome behavioural responses to the MAOI tranylcypromine and the serotonin precursor 5-hydroxy-L-tryptophan (5-HTP). As numerous case reports implicate the atypical opioids tramadol and meperidine in the development of the human serotonin syndrome, we examined tramadol and meperidine as possible causative drugs in the rodent model of the serotonin syndrome in SERT wild-type (+/+), heterozygous (+/x) and knockout (x/x) mice. Comparisons were made with SERT mice treated with either vehicle or morphine, an opioid not implicated in the serotonin syndrome in humans. Here we show that tramadol and meperidine, but not morphine, induce serotonin syndrome-like behaviours in mice, and we show that this response is exaggerated in mice lacking one or two copies of SERT. The exaggerated response to tramadol in SERT-x/x mice was blocked by pretreatment with the 5-HT1A antagonist WAY 100635. Further, we show that morphine-, meperidine- and tramadol-induced analgesia is markedly decreased in SERT-x/x mice. These studies suggest that caution seems warranted in prescribing or not warning patients receiving SSRIs or MAOIs that dangerous side-effects may occur during concurrent use of tramadol and similar agents. These findings suggest that it is conceivable that there might be increased vulnerability in individuals with SERT polymorphisms that may reduce SERT by more than 50%, the level in SERT+x/x mice.

Received 24 October 2008; Reviewed 10 December 2008; Revised 21 January 2009; Accepted 26 January 2009; First published online 11 March 2009

Key words: Hot-plate analgesia, meperidine, morphine, serotonin syndrome, serotonin transporter knockout mice, tramadol.

Introduction
The serotonin syndrome typically occurs following combinations of serotonin-enhancing drugs, including frequently prescribed antidepressants such as selective serotonin reuptake inhibitors (SSRIs) and monoamine oxidase inhibitors (MAOIs), taken even weeks apart (Gillman, 2006; Isbister & Buckley, 2005). Numerous case reports also implicate atypical opioids, including tramadol and meperidine (pethidine), as causative drugs in the serotonin syndrome (Altman & Manos, 2007; Choong & Ghiculescu, 2008; Das et al. 2008; Dougherty et al. 2002; Garrett, 2004; Gillman, 2005; Gnanadesigan et al. 2005; Houlihan, 2004; Kesavan & Sobala, 1999; Lantz et al. 1998; Mason & Blackburn, 1997; Mittino et al. 2004; Tissot, 2003; Vizcaychipi et al. 2007). In addition to their relatively weak actions on opioid receptors, tramadol, meperidine and other atypical opioids affect the reuptake and release of serotonin and norepinephrine (Dayer et al. 1994; Hennies et al. 1982; Raffa et al. 1992). (+)-Tramadol is a racemic mixture of (+)-tramadol, which has weak effects at μ-opioid receptors ($K_i=2.1 \mu M$).
and reduces serotonin reuptake ($K_i=0.99 \mu M$), and
(−)-tramadol, which reduces norepinephrine uptake
($K_i=0.79 \mu M$) (Bamigbade et al. 1997; Driessen &
In the rodent model of the serotonin syndrome,
serotonin-enhancing drugs induce behaviours including
head weaving, forepaw treading, backward movement,
low body posture, hind-limb abduction and
tremor (Izumi et al. 2006; Kennett et al. 1985; Sternbach,
1991). We recently reported a genetic mouse model for
the serotonin syndrome, as constitutive serotonin
transporter (SERT)-deficient mice produced by homologous
recombination in embryonic stem (ES) cells have exaggerated serotonin syndrome behavioural
responses to serotonin-enhancing drugs including
the MAOI tranylcypromine and the serotonin precursor 5-hydroxy-L-tryptophan (5-HTP) (Fox et al. 2007,
2008). To our knowledge, the ability of tramadol
and related agents to induce serotonin syndrome
behaviours in rodents has not been experimentally
evaluated.
In the present study, we examined tramadol and
meperidine as possible causative drugs in the rodent
model of the serotonin syndrome in SERT wild-type
(+/+), heterozygous (+/−) and knockout (−/−) mice,
and comparisons were made with SERT mice
which have either vehicle or morphine, an opioid not
implicated in the serotonin syndrome in humans
(Gillman, 2005).
Serotonin syndrome behaviours in mice, including
the exaggerated 5-HTP-induced serotonin syndrome
behavioural responses in SERT-deficient mice (Fox et al.
2007), are mediated by post-synaptic 5-HT$_{1A}$ receptors
(Lucki et al. 1984; Smith & Peroutka, 1986; Yamada et al.
1988). As tramadol is known to have some effects at
5-HT$_{1A}$ receptors (Berrocoso et al. 2006; Rojas-Corrales
et al. 2000, 2005), we also determined the possible contribution of 5-HT$_{1A}$ receptors in tramadol-induced
serotonin syndrome behaviours in SERT-deficient mice.
Finally, as tramadol is a frequently prescribed and
effective analgesic medication, we also determined the
analgesic effects of tramadol, in addition to meperidine and morphine, in SERT-deficient mice.

Materials and methods

Animals
Subjects were female SERT mice (+/+, +/− and
−/−) produced by homologous recombination in
ES cells as previously described (Bengel et al. 1998),
and currently the product of ~20–24 heterozygous
backcrosses with wild-type mice on a C57BL/6J
genetic background. Female C57BL/6J mice were
purchased from the Jackson Laboratory (USA). The
animals weighed ~20–35 g at the beginning of the
experiments, and were housed in groups of 3–5 per
cage with food and water available ad libitum. The
animals were maintained on a 12-h light/dark cycle
(9:00–21:00 hours) in a facility approved by the
American Association for Accreditation of Laboratory
Animal Care. All experiments adhered to the guide-
lines of the National Institutes of Health, and were
approved by the National Institute of Mental Health
Animal Care and Use Committee.

Drugs

(±)-Tramadol, meperidine, morphine and the selective
5-HT$_{1A}$ receptor antagonist N-[2-[4-(2-methoxyphenyl)]-
1-piperazinyl]ethyl]-N-2-pyridinylcyclohexanecarbox-
amide maleate salt (WAY 100635) were purchased
from Sigma Chemical Company (St Louis, USA). All
drugs were prepared in saline and were administered
by intraperitoneal (i.p.) injection.

Procedure

On test days, animals were moved to the testing room
in their home cage 1 h prior to testing to allow for ha-
bituation to the environment. All experiments were
carried out between 10:00 and 13:00 hours.

Serotonin syndrome behaviours

Animals were placed in a large Plexiglas cylinder, and
after 15 min of habituation were administered vehicle,
tramadol, meperidine or morphine (60 mg/kg for each of
these drugs). When 5-HT$_{1A}$ mediation of tramadol-
induced behavioural changes was examined, mice
were pretreated with either vehicle or the selective
5-HT$_{1A}$ antagonist WAY 100635 (1 mg/kg) 30 min
prior to tramadol (60 mg/kg). This dose of WAY
100635 was selected based on previous studies (Fox
et al. 2007, 2008). Behavioural assessments were made
based on previous methods (Fox et al. 2007, 2008;
Izumi et al. 2006; Kennett et al. 1985). Specifically,
behaviours associated with the rodent serotonin syn-
drome were recorded for five 1-min periods at 5-min
intervals starting 5 min after drug administration
for 30 min. In each assessment period, the following
behaviours were recorded: (a) intermittent behaviours
including head weaving, forepaw treading and back-
ward movement (scored on a 5-point scale; 0 = absent,
1 = present once, 2 = present several times, 3 = present
frequently, 4 = present continuously); (b) continuous
behaviours included hind-limb abduction, tremor and
low body posture (scored on a 5-point scale; 0 = absent,
The scores from the five 1-min periods were summed together for each individual behaviour. Overall serotonin syndrome scores were also calculated for each 5-min assessment, consisting of the sum of scores for all intermittent and continuous behaviours (Fox et al. 2007; Jacobs, 1976). As morphine and other opioids are known to induce Straub tail (Aceto et al. 1969; Belknap et al. 1989), scores for Straub tail are presented separately. Straub tail was assessed in the same manner as other continuous behaviours described above. Behavioural assessments were performed by observers blind to both the genotype and the drug condition.

**Hot-plate analgesia**

Analgesia was assessed using the hot-plate test. The hot-plate apparatus (Columbus Instruments, USA) was maintained at 55.0 ± 0.1 °C, and was surrounded by a Plexiglas enclosure. Mice were placed individually on the hot plate, and the latency to lick their hind paw or jump was measured. Mice were removed immediately after a response was made, with a 30 s cut-off if no response occurred. Data are presented as the percent of the maximum possible effect (MPE):

\[
\text{%MPE} = \left( \frac{\text{test latency} - \text{average baseline latency}}{\text{30 s cut-off} - \text{average baseline latency}} \right) \times 100
\]

where the average baseline latency is the average of three baseline assessments taken prior to drug administration. Following the baseline assessments, mice were administered vehicle or morphine (30 mg/kg), tramadol (60 mg/kg) or meperidine (30 mg/kg) and analgesia was assessed every 15 min over a 45-min period. These doses were selected based on dose–response pilot studies performed in our laboratory (data not shown). The data presented are for the time-point where analgesia was greatest in SERT +/+ mice (morphine, 45 min; meperidine, 15 min; tramadol, 15 min).

**Statistical analyses**

For each experiment, data were analysed using one- or two-way (genotype × drug condition) analyses of variance (ANOVAs). Significant main effects (one-way ANOVAs) or significant interactions (two-way ANOVAs) were followed by post-hoc comparisons between genotypes or between drug conditions using Tukey’s HSD pairwise comparisons. Significance was based on \( p < 0.05 \).

**Results**

**Serotonin syndrome behaviours**

For serotonin syndrome behaviours overall, there was a significant genotype × drug interaction \( [F(6, 105) = 2.98, p = 0.01] \) and significant main effects for genotype \( [F(2, 105) = 21.56, p < 0.0001] \) and for drug \( [F(3, 105) = 45.31, p < 0.0001] \). Compared to their respective counterparts administered vehicle or morphine, SERT mice (+/+, +/− and −/−) administered either tramadol or meperidine displayed increased levels of serotonin syndrome behaviour overall (Fig. 1). This response was exaggerated in SERT +/+ (\( p = 0.023 \)) and SERT −/− mice (\( p = 0.008 \)) administered tramadol, and in SERT −/− mice administered meperidine (\( p = 0.001 \)).
Data represent the mean ± S.E.M., n = 8–13 per group.

* p < 0.05, ** p < 0.01 compared to SERT+/+ mice (Tukey post-hoc tests).

d compared to SERT+/+ mice administered the same drug (Fig. 1). Consistent with previous reports (Fox et al. 2007; Kalueff et al. 2007), vehicle-treated SERT−/− mice displayed enhanced baseline serotonin syndrome behaviours compared to vehicle-treated SERT+/+ mice (p = 0.01). SERT−/− mice administered morphine displayed more serotonin syndrome behaviours overall than SERT+/+ mice (p = 0.006). However, the response in morphine-treated SERT−/− mice was not different from the response in vehicle-treated SERT−/− mice.

Regarding individual serotonin syndrome behaviours, tramadol-treated SERT+/− mice displayed more hind-limb abduction (p = 0.026) and low posture (p = 0.024) than SERT+/+ mice, and tramadol-treated SERT−/− mice displayed more head weaving (p = 0.024), backward movement (p = 0.015) and hind-limb abduction (p = 0.005) than SERT+/+ mice (Table 1). In meperidine-treated mice, SERT−/− mice displayed more hind-limb abduction (p = 0.033), tremor (p = 0.004) and low posture (p = 0.002) compared to SERT+/+ mice (Table 1).

The data for Straub tail are presented in Table 2. As hypothesized, morphine, tramadol and meperidine induced Straub tail in mice of all three genotypes compared to their respective vehicle-treated controls [main effect of genotype: F(2, 105) = 0.31, n.s.; main effect of drug: F(3, 105) = 82.69, p < 0.0001; genotype × drug interaction: F(6, 105) = 2.81, p = 0.014].

**Effects of the selective 5-HT1A antagonist WAY 106635 on tramadol-induced serotonin syndrome behaviours**

For the overall serotonin syndrome behavioural scores in a first study in purchased wild-type C57BL/6J mice, there was a significant main effect for drug [F(8, 18) = 17.96, p < 0.0001]. Tramadol again increased serotonin syndrome behaviours compared to vehicle-treated mice (p < 0.0001). Pretreatment with WAY 106635 had no effect on tramadol-induced behaviours in purchased wild-type mice (drug, mean ± S.D.) (vehicle: 6.1 ± 1.56; WAY 106635: 4.92 ± 2.99; vehicle + tramadol: 27.80 ± 9.50; WAY 106635 + tramadol: 25.33 ± 8.96).

In a separate study in SERT+/− and SERT−/− mice, there was a significant genotype × drug interaction for the overall serotonin syndrome behaviour scores [F(3, 54) = 5.85, p = 0.002], with a significant main effect for drug [F(3, 54) = 19.52, p < 0.0001] but not for genotype [F(1, 54) = 0.37, n.s.]. Again, tramadol induced serotonin syndrome behaviours in SERT+/− and SERT−/− mice compared to their vehicle-treated counterparts (Fig. 2). In SERT−/− mice, pretreatment with WAY 106635 decreased tramadol-induced behaviours to levels closely approximating those observed in vehicle-treated SERT−/− mice, suggesting that 5-HT1A receptors mediate tramadol-induced serotonin...
Table 2. Straub tail (sum of scores) in SERT +/+ , +/– and −/− mice administered vehicle, morphine, tramadol or meperidine

<table>
<thead>
<tr>
<th>Drug</th>
<th>SERT+/+</th>
<th>SERT+/−</th>
<th>SERT−/−</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle</td>
<td>0.22 ± 0.26</td>
<td>0.00 ± 0.00</td>
<td>0.94 ± 1.49</td>
</tr>
<tr>
<td>Morphine</td>
<td>14.44 ± 4.71</td>
<td>17.33 ± 2.54</td>
<td>12.67 ± 3.82</td>
</tr>
<tr>
<td>Tramadol</td>
<td>8.88 ± 4.87</td>
<td>6.35 ± 4.25</td>
<td>10.19 ± 3.47</td>
</tr>
<tr>
<td>Meperidine</td>
<td>11.38 ± 2.85</td>
<td>10.75 ± 4.09</td>
<td>13.06 ± 4.24</td>
</tr>
</tbody>
</table>

Data represent the mean ± S.E.M.; n = 8–13 per group. + + p < 0.01, + + + p < 0.001 compared to vehicle-treated mice of the same genotype; * p < 0.05, ** p < 0.001 compared to tramadol-treated mice of the same genotype; * * p < 0.01 compared to meperidine-treated mice of the same genotype (Tukey post-hoc tests).

Fig. 2. Overall serotonin syndrome behaviours (sum of scores) in SERT +/+ (■) and SERT−/− (□) mice administered vehicle, WAY 100635, vehicle + tramadol, or WAY 100635 + tramadol. Data represent the mean ± S.E.M., n = 5–8 per group. * p < 0.05, ** p < 0.01 compared to SERT+/− mice in the same drug condition; † p < 0.05, ††† p < 0.001 compared to mice of the same genotype administered vehicle; ‡ p < 0.01, # p < 0.001 compared to mice of the same genotype administered WAY 100635; § p < 0.05 compared to mice treated with vehicle + tramadol.

Fig. 3. Baseline hot-plate responses in SERT +/+ (■), SERT +/− (△) and SERT−/− (□) mice. Data represent the mean latency (percent of the maximum possible effect; % MPE) ± S.E.M., data combined from all analgesia studies.

**F**[(2, 27)] = 5.08, *p* = 0.014, tramadol [**F**[(2, 31)] = 3.68, *p* = 0.038] and meperidine [**F**[(2, 28)] = 3.98, *p* = 0.031]. In SERT−/− mice, morphine- (p = 0.014) and tramadol- (p = 0.045) induced analgesia were decreased ~64% and ~58%, respectively, compared to SERT+/- mice, and meperidine-induced analgesia was decreased ~65% compared to SERT+/- mice (p = 0.027) (Fig. 4). There was also a strong trend towards decreased morphine-induced analgesia in SERT+/- mice compared to SERT+/- mice (p = 0.065).

**Discussion**

In the present study, we provide the first experimental evidence that the atypical opioids tramadol and meperidine induce serotonin syndrome-like behaviours in mice, and show that this response is exaggerated in mice lacking one or two copies of SERT (Fig. 1). Functional polymorphisms in SERT in humans, such as the SERT-linked polymorphic region (5-HTTLPR) and single nucleotide polymorphisms (SNPs) within it, can reduce SERT expression and its...
function by \( \sim 50\% \) or more (Hu et al. 2006; Lesch et al. 1996; Praschak-Rieder et al. 2007), similar to levels in SERT\(^{+/−}\) mice. As such, the current findings might suggest an increased vulnerability to development of the serotonin syndrome in individuals with less-expressing SERT polymorphisms when taking tramadol or similar agents.

The serotonin syndrome is a not infrequent and potentially lethal side-effect of serotonin-enhancing drugs (such as SSRIs and MAOIs), which is associated with neuromuscular hyperactivity (e.g. tremor, myoclonus), autonomic hyperactivity (e.g. fever) and altered mental status (Dunkley et al. 2003; Gillman, 2006; Sternbach, 1991). As described, numerous case reports also implicate atypical opioids, including tramadol and meperidine, in the development of the serotonin syndrome. Such cases include individuals taking tramadol or meperidine in combination with other serotonin-enhancing drugs, including SSRIs and MAOIs (see Introduction). Importantly, a recent study shows a significant incidence of co-prescription of tramadol with MAOIs, SSRIs and other serotonin-enhancing drugs (Ringland et al. 2008). In this retrospective assessment of medical claims over a 4-yr period, \( \sim 8\% \) of this population (\( \sim 20,658 \) individuals) evidenced at least one incident of potential concurrent use of serotonergic medication combinations. Among the most common were tramadol with a SSRI or moclobemide, a reversible inhibitor of monoamine oxidase-A (RIMA) (Ringland et al. 2008).

In the present study, pretreatment with WAY 100635 did not alter serotonin syndrome behaviours observed in wild-type mice. In SERT\(^{+/−}\) mice, which displayed exaggerated serotonin syndrome behavioural responses to tramadol, WAY 100635 pretreatment was also without effect. However, the exaggerated tramadol-induced serotonin syndrome behavioural response in SERT\(^{−/−}\) mice was significantly attenuated by pretreatment with WAY 100635, suggesting mediation at post-synaptic 5-HT\(_{1A}\) receptors, known to regulate these behaviours in wild-type mice (Lucki et al. 1984; Smith & Peroutka, 1986; Yamada et al. 1988), and the exaggerated 5-HTP-induced serotonin syndrome behavioural responses previously reported in SERT\(^{−/−}\) mice (Fox et al. 2007). Together, these findings suggest that another mechanism underlies this exaggerated response in SERT\(^{+/−}\) mice, a mechanism which is of importance to explore, and will require further studies. One possibility is that tramadol might be inducing this exaggerated serotonin syndrome behavioural response in SERT\(^{+/−}\) mice by blocking SERT, thus increasing extracellular levels of serotonin, rather than by directly activating postsynaptic 5-HT\(_{1A}\) receptors, which appears to underlie this response in SERT\(^{−/−}\) mice. However, the site of action of these elevated serotonin levels in SERT\(^{+/−}\) mice remains to be elucidated.

Tramadol is an effective analgesic medication, with fewer side-effects and lower abuse potential than more traditional opioids such as morphine. In the first tests of opioid analgesia in genetically deficient SERT mice, we report that morphine-, meperidine- and tramadol-induced analgesia is markedly decreased in SERT\(^{−/−}\) mice, with a strong trend towards a decrease in morphine-induced analgesia in SERT\(^{+/−}\) mice (Fig. 4). The mechanisms underlying the decreased analgesic effects of these typical and atypical opioids in SERT-deficient mice remain to be elucidated, but would seem to be of high interest.

There appear to be several different mechanisms of action underlying the analgesic effects of tramadol, which probably interact, and which are probably species and paradigm specific. For example, although the non-selective opioid antagonist naloxone decreases the analgesic effects of tramadol in humans (Desmeules et al. 1996) and in rodents (Berrococo et al. 2007; Raffa et al. 1992), this effect is only partial in some assessments. Further, tramadol retains its analgesic effects in \( \mu \)-opioid knockout mice, an effect decreased in a gene-dose dependent manner (Ide et al. 2007).
2006). These studies suggest that the analgesic effects of tramadol are not solely mediated by the opioid system. To our knowledge, the number, binding and function of opioid receptors have not been examined in SERT-deficient mice.

A role for the norepinephrine system has also been described, as the α2-adrenoceptor antagonist yohimbine blocks tramadol-induced analgesia (Raffa et al. 1992), including the residual response in μ-opioid knockout mice (Ide et al. 2006) in some analgesia paradigms. Other studies show that tramadol analgesia is markedly enhanced in α2A-adrenoceptor knockout mice (blocked by naloxone), and that the α2-adrenoceptor antagonists yohimbine and atipamezole potentiated the analgesic effects of tramadol in wild-type mice (Ozdogan et al. 2006). The only investigations of the norepinephrine system in SERT-deficient mice show that the anti-immobility effects of the norepinephrine transporter (NET) blocker desipramine and the SERT/NET blocker imipramine of the norepinephrine transporter (NET) blocker deficiet mice show that the anti-immobility effects of tramadol are not solely mediated by the opioid system. To our knowledge, the number, binding and function of opioid receptors have not been examined in SERT-deficient mice.

Roles for the serotonin system have also been noted in tramadol’s actions. For example, the selective 5-HT1A antagonist WAY 100635 (Berrocoso et al. 2006, 2007; Rojas-Corrcoles et al. 2005) and the 5-HT1A antagonist/β-adrenoceptor antagonist pindolol (Rojas-Corrcoles et al. 2000) increase the analgesic effects of tramadol, whereas the 5-HT1A agonist 8-OH-DPAT decreases tramadol-induced analgesia (Berrocoso et al. 2007; Rojas-Corrcoles et al. 2000). Yet other studies suggest a role for 5-HT2A receptors in tramadol-induced analgesia (Oliva et al. 2002; Xie et al. 2008). Numerous studies show alterations in several of serotonin’s 14-plus receptor subtypes in SERT-deficient mice, including decreased number and function of presynaptic 5-HT1A receptors (Bouali et al. 2003; Fox et al. 2008; Holmes et al. 2003; Li et al. 1999, 2000) and brain-area-dependent changes in 5-HT2A binding and function (Basselin et al. 2009; Li et al. 2003; Qu et al. 2005; Rioux et al. 1999).

Further studies are required in order to determine the mechanism underlying the decreased analgesic responses to tramadol, meperidine and morphine in SERT-deficient mice. For example, it will be of importance to determine the effects of pretreatment with 5-HT1A antagonists such as WAY 100635 and α2-adrenoceptor antagonists such as yohimbine on opioid-induced analgesia in SERT mice (+/+, +/− and −/−).

Several studies report that in addition to its analgesic effects, tramadol has effects in animal models of several psychiatric disorders. Tramadol is effective in animal models predictive of antidepressant efficacy; e.g. tramadol decreases immobility in the forced swim test and reverses the physical and behavioural alterations induced by unpredictable chronic mild stress (Berrocoso et al. 2006; Rojas-Corrcoles et al. 1998, 2002, 2004; Yalcin et al. 2005, 2007, 2008). Additionally, tramadol blocks the head-twitch response in mice induced by the serotonin precursor 5-HTP and the 5-HT2A/2C agonist (±)-2,5-dimethoxy-4-methylamphetamine (DOM) (Rojas-Corrcoles et al. 2007; Sun et al. 2003), suggested as an animal model for tics and Tourette syndrome (Dursun & Handley, 1996; Gaynor & Handley, 2001; Hayslett & Tizabi, 2005).

Importantly, findings in humans also suggest that tramadol may be an effective treatment in several neuropsychiatric illnesses, in particular in some patients who are refractory to traditional treatments. Specifically, these studies suggest that tramadol might be effective in treating depression (Reeves & Cox, 2008; Shapira et al. 2001; Spencer, 2000), potentiating the antidepressant effects of other medications including SSRIs (Fanelli & Montgomery, 1998), decreasing suicidal ideation (Spencer, 2000) and in treating obsessive–compulsive disorder (OCD) and Tourette syndrome (Goldsmith et al. 1999; Shapira et al. 1997a, b, 2001).

The current findings are important, as they suggest caution when using tramadol in the treatment of, or to augment SSRIs or other antidepressants in the treatment of, pain, depression, OCD, Tourette syndrome and other psychiatric disorders where these pro-serotonergic agents might be employed (Fanelli & Montgomery, 1998; Goldsmith et al. 1999; Reeves & Cox, 2008; Shapira et al. 1997a, b, 2001; Spencer, 2000). Similarly, caution seems warranted in prescribing or not warning patients receiving SSRIs or MAOIs, that dangerous side-effects may occur during concurrent use of tramadol and similar agents for their analgesic actions (Ringland et al. 2008). The current findings also suggest caution when prescribing tramadol and other atypical opioid medications to individuals with the
S or SS 5-HTTLPR, SERT polymorphisms that may reduce SERT by more than 50% (Hu et al. 2006; Lesch et al. 1996; Prasad et al. 2005), as these individuals might be at higher risk for developing the serotonin syndrome. Further, within this genetic mouse model, it is of high importance to investigate the effects of other drugs implicated in human cases of the serotonin syndrome, such as the antibiotic linezolid (Das et al. 2008; Packer & Berman, 2007), triptans used in the treatment of migraine (Bonetto et al. 2007), as well as St John’s Wort and other over-the-counter herbal remedies (Bonetto et al. 2007; Dannawi, 2002; Parker et al. 2001).

Acknowledgements

This research was supported by the NIMH Intramural Research program. The authors thank Su-Jan Huang and Teresa Tolliver for their continued assistance with animal care and genotyping.

Statement of Interest

None.

References


