THE EFFECT OF VENLAFAXINE ON FUNCTIONAL RECOVERY FOLLOWING SPINAL CORD INJURY

by

DON E. MCCORMICK

CANDACE L. FLOYD, COMMITTEE CHAIR
C. SCOTT BICKEL
AMIE B. JACKSON
PETER R. SMITH

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THE EFFECT OF VENLAFAXINE ON FUNCTIONAL RECOVERY FOLLOWING SPINAL CORD INJURY

DON E. MCCORMICK

BASIC MEDICAL SCIENCE

ABSTRACT

Spinal cord injury (SCI) can significantly alter a person’s physical and psychological health over their lifetime. Depression in persons with SCI is often treated with antidepressants which alter serotonergic and adrenergic signaling, both regulators of plasticity. However, the effects of antidepressants functional recovery after SCI have never been evaluated. Therefore, we hypothesize that antidepressant therapy would alter functional recovery and neuropathic pain behaviors in a SCI rodent model.

The aim of this study was to evaluate the effects of venlafaxine (VEN) administration on functional recovery in the rehabilitation setting using a SCI rodent model. Adult male Sprague-Dawley rats received a moderate contusion T10 SCI. Therapeutic intervention began at day 31 post-SCI and continued for 30 days, after which the animals were euthanized and spinal tissue was harvested for histological evaluation. Animals were randomly to receive either VEN daily, weekly rehabilitation (REHAB), both (VEN/REHAB), or neither as a control (CTRL). Functional recovery was evaluated with the Basso, Beattie, and Bresnahan open-field test, the CatWalk® kinematic analysis, and the Louisville swim scale. Neuropathic pain was assessed using both the tail-flick test and von Frey filament. Depression was evaluated with the Porsolt forced swim test prior to and after the therapeutic interventions.

We found that the group receiving the REHAB intervention alone had significantly increased hind limb function and decreased pain when compared to CTRL,
and the benefits of REHAB on motor function were not seen in the VEN/REHAB group. VEN alone had no effect on either pain or functional recovery. These data suggest that VEN treatment hinders the spinal plasticity and locomotor recovery gained from REHAB, while having no effects on pain. Another interesting finding seen in groups receiving VEN is a significant increase in the incidence of priapism. Finally, the Porsolt forced swim test showed no differences in depressive behaviors between groups, which brings into question the efficacy of VEN for alleviating depressive symptoms in a SCI patient. Therefore, our findings suggest that antidepressant therapy in an SCI model fails to alter depressive behaviors, while preventing functional gains from rehabilitation and causing the untoward side effect of priapism.

Keywords: antidepressant, rehabilitation, priapism, neuropathic pain, neurotrauma
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<tr>
<td>5-HT</td>
<td>serotonin</td>
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<tr>
<td>BBB</td>
<td>Basso, Beattie, and Bresnahan open-field test</td>
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<tr>
<td>CNS</td>
<td>central nervous system</td>
</tr>
<tr>
<td>CTRL</td>
<td>control</td>
</tr>
<tr>
<td>EMG</td>
<td>electromyography</td>
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<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
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<tr>
<td>HED</td>
<td>human equivalent dose</td>
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<td>IP</td>
<td>intraperitoneal</td>
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<tr>
<td>LSS</td>
<td>Louisville swim scale</td>
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<tr>
<td>MPE</td>
<td>maximal possible effect</td>
</tr>
<tr>
<td>NE</td>
<td>norepinephrine</td>
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<tr>
<td>PWT</td>
<td>paw withdrawal threshold</td>
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<tr>
<td>REHAB</td>
<td>rehabilitation</td>
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<td>SCI</td>
<td>spinal cord injury</td>
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<tr>
<td>SEM</td>
<td>standard error of the mean</td>
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<tr>
<td>SNRI</td>
<td>serotonin–norepinephrine reuptake inhibitors</td>
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<td>SSRI</td>
<td>selective serotonin re-uptake inhibitors</td>
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<tr>
<td>TTH</td>
<td>time to helplessness</td>
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<tr>
<td>VEN</td>
<td>venlafaxine</td>
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INTRODUCTION

Traumatic SCI is a debilitating condition that can significantly affect a person’s physical and psychological health over a lifetime. Indeed, studies suggest that symptoms of depression and anxiety are common in both the acute and chronic setting after SCI with an estimated 20-43% of persons with SCI being at risk of developing a depressive disorder during rehabilitation and 16-60% of persons with SCI experiencing depression of clinical significance when living in the community (Elliot et al, 1996; Kennedy and Rogers, 2000; Dryden et al, 2005; Craig et al, 2009). Although the underlying neurobiology of depression after SCI is poorly understood, there is general agreement in the clinical community that these psychological complications are associated with poor outcome. Clinicians are therefore motivated to treat depression and anxiety in persons with SCI typically by prescribing antidepressants, but the effects of these medications in persons with SCI have not been rigorously evaluated. This is of concern, since antidepressant medications alter central nervous system (CNS) neurochemistry, including serotonergic and adrenergic signaling, both of which are critical regulators of plasticity and functional recovery following SCI. Consequently, we propose to evaluate the effects of antidepressant administration after SCI using a pre-clinical rodent model.

The antidepressant compound we have selected to evaluate is the highly-prescribed venlafaxine (VEN), or EFFEXOR®, which is a serotonin-norepinephrine reuptake inhibitor (SNRI) that increases CNS levels of serotonin (5-HT) and
norepinephrine (NE). VEN has an added benefit for use in persons with SCI in that it
does not exacerbate spasticity like other antidepressants including most SSRIs (Stolp-
Smith and Wainberg 1999; del Real et al 1996). However, the effects of VEN
administration on depression and anxiety after SCI have never been evaluated in
controlled clinical trials or in pre-clinical studies. Additionally since VEN alters CNS 5-
HT and NE signaling, we hypothesize that post-SCI administration of VEN could alter
functional recovery after SCI by pharmacological stimulation of plastic changes in
sensorimotor and reflexive circuitry below the level of the injury. Both NE and 5-HT
have been shown to play roles in spinal cord circuitry-controlled locomotion. For
example, the NE agonist clonidine is highly effective in inducing full weight bearing
steps in spinalized cats (Edgerton et al, 2004), yet clonidine has shown a depressive
effect on EMG activity in complete SCI patients during treadmill walking (Edgerton et al,
2004). Also, a 5-HT$_{2C}$ agonist dramatically increased weight supported steps in rats with
spinal transections (Kim et al, 2001). Interestingly, both 5-HT and NE have been shown
to increase motor neuron excitability by facilitating persistent inward currents via 5-HT$_{2C}$
and $\alpha_1$-receptors, respectively (Murray et al 2010; Rank et al, 2011). Additionally, NE
can inhibit polysynaptic flexor reflexes by acting on $\alpha_2$-receptors on sensory afferent
nerves, which may account for reduced reports of exacerbation of spasticity by SNRIs
when compared to SSRIs (Rank et al, 2011). It has been shown in a rat model that motor
neurons increase their excitability in response to the loss of descending serotonergic input
following SCI by altering isoform expression of the 5-HT$_{2C}$ receptors. Following the loss
of 5-HT input, denervated motor neurons respond by altering post-translational editing of
mRNA encoding the 5-HT$_{2C}$ receptor in a way that upregulates the expression of a
constitutively active isoform, resulting in calcium influx in the absence of 5-HT, in turn increasing excitability of the motor neuron (Murray et al 2010). It will be important to investigate what effects an SNRI such as VEN, that alters synaptic levels of both of these neurotransmitters, has on recovery and the resulting expression of the key receptors mentioned above.

In the spinal cord, the control of both motor neuron excitability and sensory transmission depends on descending monoaminergic drive, including NE and 5-HT, originating primarily from the brainstem and providing the spinal cord with a state-dependent control of excitability (Rank et al, 2011). Following SCI, levels of these monoamines in the spinal cord remain significantly reduced due to the severance of the axons that carry them from the brainstem. (Hains et al, 2002). Monoamine transporters play an important role in maintaining proper levels of these neurotransmitters in the spinal cord by sodium-dependent re-accumulation of released neurotransmitters into pre-synaptic terminals (Uhl and Johnson, 1994). Studies in a rat model have indicated that following SCI, surviving serotonergic axons respond to the decreased availability of 5-HT by up-regulating expression of the 5-HT transporters to increase the recycling of 5-HT (Hains et al, 2002). This is problematic, since these are the very transporters which are inhibited by antidepressant therapy; antidepressants may further deplete levels of these monoamines regulating neuron excitability below level of the lesion. Bosker et al (2010) showed that after 17 days of SSRI therapy in a rat model, brain 5-HT levels were depleted by more than 50%. Therefore, it is likely that reuptake inhibitors may cause similar neurotransmitter depletion in the spinal cord, perhaps further impairing monoamine signaling below the lesion following SCI.
Despite the inability to regenerate axons in the CNS, patients with incomplete SCI have been documented to spontaneously recover both motor and sensory function, indicating that recovery in some form can occur. The various mechanisms of this recovery develop over weeks in the rat model and over months in humans. During initial recovery post-SCI, spared axons recover from spinal shock, or are remyelinated following myelin sheath loss due to the death of oligodendrocytes immediately post-injury (Fouad and Tse, 2008). Further recovery is due to plasticity of the nervous system, which includes axonal sprouting, synaptic rearrangements, and changes in neuronal chemistry. Spared axons are known to sprout to neighboring motor neurons in the ventral horns, which correlates with greater functional recovery (Fouad and Tse, 2008; Lynskey et al, 2008). However, it is unknown what effects increased synaptic levels of NE and 5-HT via reuptake blockade will have on plasticity and ultimately functional recovery.

Although there is a high prevalence of depression in the SCI patient population, the effects of antidepressant therapy on functional recovery have not been rigorously evaluated. Human trials to investigate the effects of antidepressants would require placebo controls in the form of withholding treatment for depression from a recovering SCI patient. On the other hand, using a rodent SCI model allows us to gain insight into the possible effects of antidepressants on recovery following SCI. We hypothesized that administration of VEN at a clinically relevant dose in the chronic period after SCI would alter psychological health, functional recovery, and neuropathic pain in a rodent SCI model.
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DON E. MCCORMICK, TRACY A. NEIDZELKO, AND CANDACE L. FLOYD

DEPARTMENT OF PHYSICAL MEDICINE AND REHABILITATION
UNIVERSITY OF ALABAMA AT BIRMINGHAM
BIRMINGHAM, AL

Corresponding Author:
Candace L. Floyd, Ph.D.
Assistant Professor
Department of Physical Medicine and Rehabilitation
Spain Rehabilitation Center 546
University of Alabama at Birmingham
clfloyd@uab.edu
205-996-6892
THE EFFECT OF VENLAFAXINE ON FUNCTIONAL RECOVERY FOLLOWING SPINAL CORD INJURY

Abstract

Introduction

Spinal Cord Injury (SCI) can significantly alter a person’s physical and psychological health. Depression in persons with SCI is often treated with antidepressants which alter serotonergic and adrenergic signaling, both critical regulators of plasticity. However, the effect of antidepressants on plasticity and functional recovery after SCI has never been evaluated.

Methods

The aim of this study was to evaluate the effects of venlafaxine (VEN) administration on functional recovery in the rehabilitation setting using a SCI rodent model. Venlafaxine is a serotonin-norepinephrine reuptake inhibitor. Adult male Sprague-Dawley rats were subjected to a moderate contusion SCI at the T10 level. Therapeutic intervention began at day 30 post-SCI and continued for 30 days, after which the animals were euthanized and spinal tissue was harvested for histological
evaluation. Each animal received two intervention variables, either daily administration of VEN or water as a control (CTRL), and either weekly rehabilitation (REHAB) or not. Therefore, the animals were randomly divided up so that the treatment groups were CTRL, VEN, REHAB, and VEN/REHAB. The animals were evaluated weekly for functional recovery of hindlimb locomotion using Basso, Beattie, and Bresnahan open-field test (BBB), the CatWalk® kinematic analysis, and the Louisville swim scale (LSS) with evaluations staggered to avoid fatigue. Depression was evaluated with the Porsolt forced swim test prior to and after the therapeutic interventions.

Results

Using the BBB and Catwalk kinematic analysis, we found that the group which received the REHAB intervention alone to have significantly increased function when compared to CTRL, and significance was lost in the group which received VEN/REHAB. The LSS showed a group effect of both REHAB and VEN/REHAB when compared to CTRL. No significant differences were noticed in any of the functional behavioral tests between the groups that did not receive rehabilitation (VEN vs. CTRL), suggesting no main effect of venlafaxine treatment. Additionally, the groups which received rehabilitation (REHAB and VEN/REHAB) both displayed decreased allodynic and hyperalgesic pain behaviors when compared to CTRL, with VEN having no effect. These data suggest that VEN treatment hinders the spinal plasticity and locomotor recovery gained from REHAB, while having no effects on pain. Another interesting and clinically relevant finding seen in both VEN and VEN/RHAB treatment groups is a significant
increase in the incidence of priapism when compared to the groups which did not receive VEN (CTRL and REHAB). We hypothesize this novel finding is due to the depletion of NE at sympathetic inputs to the penile tissues, a result of the reuptake inhibition of norepinephrine by VEN. Finally, the Porsolt forced swim test showed no differences in depressive behaviors between groups, which brings into question the efficacy of VEN for alleviating depressive symptoms in a SCI patient.

**Conclusions**

Taken together, these data suggest that rehabilitation is beneficial after SCI by improving locomotor function and decreasing neuropathic pain. However, administration of the antidepressant venlafaxine during rehabilitation may prevent the potential gains from the therapy while having no effect on pain. Our findings also bring into question the efficacy of VEN in treating depression in a SCI patient population. Additionally, administration of a NE reuptake inhibitor such as VEN may lead to priapism, an unwanted and possibly dangerous side effect.

**Introduction**

Traumatic spinal cord injury (SCI) is a debilitating condition that can significantly affect a person’s health, both physically and psychologically, over a lifetime. The injury usually results in permanent paralysis of voluntary muscles and loss of sensation below
the lesion, which is associated with reduced mobility and functional independence, impairment of social and vocational activities, as well as negative influences on the person's health and well-being (Elliot et al, 1996; Middleton et al, 2007). In the United States, the annual incidence of SCI is about 40 cases per million, or approximately 12,000 per year, while the 2010 estimates of prevalence of SCI patients range from 232,000-316,000 (National Spinal Cord Injury Statistical Center, 2008). Since 2005, the average age at injury has been 40.7, with 80.7% of documented SCI cases occurring in males (National Spinal Cord Injury Statistical Center, 2008). The most common cause of SCI is motor vehicle accidents (40.4%), followed by falls (27.9%) and violence (15%), with the latter mostly caused by gunshot wounds (National Spinal Cord Injury Statistical Center, 2008). Regardless of the cause of injury, the rate of depression in SCI patients is about 1 in 5, higher than the prevalence of 1 in 20 in the general population (Northwest regional SCI system, 2012). It is generally believed that depression is associated with poor outcomes following SCI. Therefore, clinicians compassionately strive to treat depression in persons with SCI typically by prescribing antidepressants, but the effects of these medications in persons with SCI have not been rigorously evaluated.

As described above, the rate of depression in SCI patients is higher than the general population, with estimates ranging from 11-37% (Northwest regional SCI system, 2012). Studies suggest that symptoms of depression are common in both the acute and chronic setting after SCI with an estimated ~30% of persons with SCI being at risk of developing a depressive disorder during rehabilitation and ~27% of persons with SCI experiencing depression of clinical significance when living in the community (Craig et al, 2009). In addition, studies have shown that persons with SCI are more likely to suffer
from depression with increasing age and greater number of years post injury (Krause et al., 2000). Therefore, many SCI patients are chronically prescribed antidepressants that alter neurochemistry in hopes of alleviating their symptoms. However, neither the efficacy nor the side effects of antidepressants in a SCI patient population has been sufficiently evaluated. Selective serotonin reuptake inhibitors (SSRI), a commonly prescribed class of antidepressants, have been documented to exacerbate spasticity in SCI patients (Stolp-Smith and Wainberg 1999). Venlafaxine (VEN), a serotonin-norepinephrine reuptake inhibitor (SNRI) is an antidepressant commonly prescribed to SCI patients as is it is not believed to increase spasticity as do SSRIs (Stolp-Smith and Wainberg 1999; del Real et al. 1996). However, it is unclear what affects altering synaptic levels of both serotonin (5-HT) and norepinephrine (NE) will have on the chronic SCI patient’s many neurological concerns.

Currently, the most widely accepted theory of depression pathology is that the cause lies in abnormalities in serotonergic signaling. Many therapies for depression over the past several decades have been designed to increase transmission of 5-HT, mainly through inhibition of its reuptake by presynaptic neurons with the intention of increasing synaptic levels of 5-HT and potentiating neurotransmission (Cryan and Leonard, 2000). Older tricyclic antidepressants, which inhibit the reuptake of both NE and 5-HT, have been mostly replaced by newer drugs with lower side-effect profiles, predominately SSRIs and SNRIs. Although it is known that drugs such as SSRIs increase synaptic levels of 5-HT, the resulting antidepressant effects may not be solely resulting from higher levels of 5-HT binding to the post-synaptic neuron. Even though blockade of 5-HT reuptake happens in a matter of minutes after drug administration, therapeutic effects
of the antidepressants are not first seen until weeks of continued therapy. One possible explanation is the observed down regulation of both the inhibitory 5-HT_{1A} postsynaptic receptor and the presynaptic 5-HT_{1B} receptors, which corresponds to the time required to reach therapeutic effects from antidepressants (Cryan and Leonard, 2000). After desensitization, the 5-HT_{1A} receptor loses its ability to inhibit firing of the post synaptic neuron, but the loss of the 5-HT_{1B} receptors’ ability to inhibit the release of 5-HT further contributes to 5-HT depletion (Cryan and Leonard, 2000). These findings have mostly resulted from studies looking exclusively at the brain in rat models, yet there is likely a similar response of the monoamine neurons in the spinal cord during chronic antidepressant therapy. Therefore, understanding the effects antidepressant therapy has on both serotonergic and adrenergic signaling is of unique importance in SCI patients, as both 5-HT and NE play numerous roles in the spinal cord.

In addition to losing sensation and motor function, 60-80% of all SCI patients experience neuropathic pain, with 40% of patients reporting relief from pain as their primary medical goal (Yezierski, 2000). Neuropathic pain presents as either allodynia, a painful response to a non-noxious stimulus, or hyperalgesia, increased pain sensitivity. It remains a challenge for health care professionals to treat neuropathic pain being that traditional pharmacological interventions, including opioid and non-opioid analgesics, have been found to be ineffective (Dworkin et al, 2007). Neuropathic pain post-SCI is partly caused by the loss of descending 5-HT inhibition of primary nociceptive afferents at the superficial dorsal horns (Hains et al, 2002). This is believed to be the reason selective 5-HT reuptake inhibitors have been shown to produce antinociceptive effects (Hains et al, 2002). Consequently, it would be relevant to further investigate the effects
VEN has on pain in an SCI model since it is a commonly prescribed medication that alters 5-HT synaptic levels.

The traditional approach to management of chronic SCI patients involves orthoses to assist in function and prevent deformities, usually without any rehabilitation intended to improve locomotor function (Lin and Cardenas, 2003). However, it has been shown after incomplete SCI in humans that rehabilitative strategies, such as intensive repetitive training and locomotor training, can promote recovery via plastic abilities of existing spinal locomotor pathways (Lynskey et al., 2008). Also, passive exercise, such as motorized cycling, promotes plasticity caudal to the injury, while active training promotes cortical rewiring to restore control of caudal circuitry (Lynskey et al., 2008).

Considerable research has been conducted to examine the effect of physical exercise as a mono- or adjunct therapy for use in anxiety and depression disorders in a wide-variety of applications in the general population (Daley 2008). A recent Cochrane Review concluded that exercise improved the symptoms of depression; however, the best type, frequency, and duration of exercise for this clinical effect have yet to be determined (Mead et al., 2009). The health benefits of exercise as a rehabilitation strategy following SCI are well documented (Duran et al., 2001; Jacobs and Nash, 2004) and many SCI rehabilitation programs contain some form of regular exercise therapy, but the efficacy of these therapeutic modalities for depression has not been evaluated in a SCI model. Thus, in this study we have examined the effects of post-SCI VEN administration in the presence or absence of exercise rehabilitation therapy.
Methods

Experimental Animals

All experimental protocols were conducted in accordance with the National Institutes of Health guidelines for the care and use of laboratory animals, and were carried out with approval from the Institutional Animal Care and Use Committee of the University of Alabama at Birmingham. The animals were adult male Sprague-Dawley rats (2 months old, 250–300 g) and were maintained on a diet of purified chow and water ad libitum. The animals were group-housed in a room with a 12-h light/dark cycle. Sixty-two animals were used to investigate the effects of both VEN therapy and physical rehabilitation on behavioral and histological outcomes following SCI with the following groups: Control (CTRL n=15), Rehabilitation (REHAB, n=15), Venlafaxine (VEN, n=16) or Rehabilitation + Venlafaxine (VEN/REHAB, n=16).

Induction of T10 Contusional SCI and Post-Operative Care

SCI was induced at the vertebral thoracic level 10 (T10) in adult male rats using the Infinite Horizons Impactor. The rats were anesthetized using 4% isoflurane in oxygen, followed by a ketamine/xyazine cocktail (100/10 mg/kg IP). The thoracic region was shaved and aseptically prepared for surgery. During surgery and for 24h thereafter body temperature was maintained with a heating pad. A two-inch incision was made centered over T10, followed by surgical laminectomy of the T10 vertebrae to expose the spinal cord. The adjacent vertebral bodies were also exposed and clamped.
with Adison forceps attached to supporting arms and a platform to stabilize the spinal column during impact. A target force of 250 kDyn to mimic moderate-severe contusional SCI that resulted in paraplegia. To assure the induced injury resulted in an appropriate functional deficit, the animals which displayed no hindlimb movement or hindlimb weight support on post-SCI day 10 were excluded (the first Basso, Beattie, Bresnahan assessment, explained later). Acute and chronic care of SCI injured animals was as previously described (Dunham, 2010). Immediately after surgery and twice daily (AM and PM) for 5 days post-SCI, the rats received subcutaneous injections of Ringer’s solution (3 mL), enrofloxacin (2.5 mg/kg; Bayer HealthCare LLC, Shawnee Mission, KA), and carprofen (5 mg/kg; Pfizer, New York, NY). Animals were inspected twice per day and weighed daily for the duration of the experiment. The bladders of paraplegic animals were manually voided 2-3 times per day by Crede’s method for the duration of the experiment. The animals were also checked for priapism twice a day, once in the morning and again in the afternoon. Presence or absence of priapism was recorded. Presence of priapism was defined as visible, blood-engorged penile tissue protruding from the animal’s foreskin prior to bladder expression.

Experimental Therapeutic Intervention

In order to study the effects of drug and rehabilitation therapies in the chronic SCI setting, both interventions began on day 31 following SCI. The rats were randomly chosen receive either VEN, or rehabilitation (REHAB), or both (VEN/REHAB), or neither intervention (CTRL). The VEN treatment groups (VEN and VEN/REHAB) were
administered 36.4 mg/kg VEN intragastrically twice daily, while the CTRL and REHAB groups received deionized water intragastrically twice per day. This dosage of VEN was converted from the typical human dose such that the conversion was calculated with two considerations: 1) mimicry of the clinically recommended starting dose for VEN of 75 mg per day divided into two or three doses (Howell et al, 1993), and 2) compensation for the species-specific metabolism of VEN and active metabolites in rats when compared to humans, as detailed below. To convert this clinical dosage of 75 mg to the equivalent rat dosage, we used the FDA recommended human equivalent dosage (HED) formula, shown below (Center for Drug Evaluation and Research, 2005). Assuming a 60 kg man and a 500 g rat, we converted the clinical dose of 75 mg to 1.25 mg/kg.

\[
\text{HED (mg/kg)} = \frac{\text{Animal dose (mg/kg)} \times [\text{animal weight (kg)} / \text{human weight (kg)}]^{0.33}}{\text{Animal dose (mg/kg)} = 1.25 \text{ mg/kg} / [0.5 \text{ kg} / 60\text{kg}]^{0.33} = 6.07 \text{ mg/kg}}
\]

The metabolism of VEN varies across different species, with O-desmethyl-venlafaxine being the major active metabolite (Howell et al, 1993). It is also reported that the percentage of a single dose of venlafaxine excreted as the parent compound or O-desmethyl-venlafaxine in a rat and man is 10.1% and 60.5%, respectively (Howell et al, 1993). In order to have our treatment consist of comparable levels of the active metabolites, we multiplied our calculated dose of 6.07 mg/kg by the percentage ratio of these active metabolite to reach a dosage of 36.4 mg/kg per day.
Table 1. Treatment groups. Intervenotional treatments consisted of two variables; either venlafaxine (VEN) or water administered intragastrically twice daily, and either weekly rehabilitation (REHAB) or no REHAB. The n for the four groups are shown.

Rehabilitation by exercise therapy was administered as previously described (Smith et al, 2006). The exercise therapy consists of both monitored shallow water walking and swimming with cutaneous feedback in a Plexiglas pool (60” long, 7” wide, and 12” deep). For the shallow water walking, the pool was filled to a depth of 2” with warm tap water (~30°C) and lined with DUPLO® plates. For the swimming with cutaneous feedback, the pool was filled to a depth of 8” with warm tap water (~30°C) and equipped with buoyant inverted centrifuge tubes suspended from the bottom of the pool to provide cutaneous feedback. The cohorts of animals undergoing rehabilitation (RHAB & VEN/REHAB) did so four days a week over the four weeks of intervention. During the first week, rehabilitation sessions began with one 4 minute swim session and increased by one session each of the four consecutive days to reach 4 sessions on day 4. For the second week of training, the rats swam a 1 x 4 min session with cutaneous feedback, followed by a single 4-min session of shallow-water walking per day each of the four
days. For intervention weeks 3 and 4, the rats completed 3 x 4 min swim sessions with cutaneous feedback, followed by 3 x 4 min sessions of shallow-water walking per day for the 4 days each week. Prior to spinal cord injury, the animals were acclimatized to the pool for 4 minutes per day for five consecutive days.

**Evaluation of Functional Recovery: BBB locomotor test**

Hind limb locomotor function after SCI injury was evaluated using the Basso, Beattie, Bresnahan (BBB) open-field locomotor test (Basso et al., 1995). Animals were placed in a 1.2-m diameter metal, smooth-surfaced activity chamber for 4 min, and hind limb movement was scored by two trained investigators who were naïve to the treatment of the animal. All discrepancies in scores were resolved by discussion between the raters at the conclusion of the test and scored to the deficit. Scores were generated for each hind limb and averaged. The scale is based on well-defined operational definitions that are used to rank hind limb movements, ranging from no movement (0) to normal walking with coordinated fore–hind limb stepping and normal paw placement (21) (Basso et al., 1995). Scores from 0 to 7 evaluate hind limb joint movements (hip, knee, and ankle) at the early stage of recovery. Scores from 8 to 13 evaluate stepping and coordination by indicating the return of paw placement and coordinated movements with the forelimbs. Scores 14–21 evaluate the return of toe clearance during stepping predominant paw position, trunk stability, and tail position. BBB scores were obtained on post-SCI days 10, 17, 24, 31, 38, 45, 52, and 59. On the first assessment, the animals must receive greater than 0 and less than 9 (weight support) to be included in the study.
**Evaluation of Functional Recovery: CatWalk Gait Analysis**

Dynamic locomotor parameters were assessed using the CatWalk gait analysis system (CatWalk 7.1; Noldus Information Technology, Leesburg, VA), as previously described by Hamers and colleagues (Hamers *et al.*, 2006; Koopmans *et al.*, 2005). Briefly, the animals traversed a glass walkway (109x15x0.6 cm) with dark plastic walls spaced 15 cm apart in a darkened room. Light from an encased fluorescent bulb was internally reflected within the glass walkway and scattered when the plantar surface of the paw contacted the walkway floor, thereby producing paw prints. The paw prints were recorded by a high-speed CCD camera mounted below the walkway, and 50 half-frames per second were stored on a computer by the associated CatWalk 7.1 acquisition software. The animals were habituated to the walkway prior to surgical manipulation. An acrylic glass enrichment house from the home cage was placed at the end of the walkway to encourage uninterrupted walkway crossings, and trials in which the animal stopped or changed direction were excluded from subsequent analysis. Pawprint designations were assigned and data were analyzed using the CatWalk analysis software (version 7.1.6). The parameters analyzed have been previously described in detail (Gabriel *et al.*, 2007; Hamers *et al.*, 2006), and included the regularity index, which is a measure of interlimb coordination. Three trials per day were analyzed and averaged to obtain a daily value. The animals were tested prior to injury and once weekly thereafter. The animals were tested on post-SCI days 9, 16, 23, 30, 37, 44, 51, and 58.
Evaluation of Functional Recovery: Louisville Swim Scale

Swimming performance was assessed using the Louisville Swim Scale (LSS) prior to injury, and post-SCI days 8, 15, 22, 29, 36, 43, 50, and 57. For each assessment, the animal swam one 4-min session and filmed by a digital camera mounted atop a tripod, in level with the water line. The swim sessions were scored by a single observer who was blinded to treatment group. During the assessments, the rats were placed at one end of the pool and picked up and transferred when they reached the opposite end with the exit ramp. The animals were acclimated to the tank prior to injury for 4 min sessions on consecutive days until the animals moved immediately to the exit ramp, usually after 2 sessions. The LSS is an 18-point scale (0–17) with three ranges—0–5, 6–11, and 12–17. The LSS was designed to evaluate swimming performance based on the three primary components of swimming described earlier, forelimb dependency, hindlimb activity and alternation, and body position (Smith 2006).

Evaluation of Hyperalgesia: Tail-Flick

The effects of VEN and REHAB interventions on thermal hyperalgesia were assessed using the tail-flick device as previously described (Dewey et al., 1970). The test consisted of placing the animal inside the enrichment house from its home cage, while infrared heat was applied to each animal’s tail, and the device recorded the latency of withdrawal from the stimulus. A baseline response was determined for each animal before injury, and test latency was determined weekly thereafter, before and during therapeutic intervention. A maximum latency of 10 s was imposed to minimize tissue
damage. Antinociceptive response was calculated as percent maximum possible effect (%MPE), where 
\[ \%MPE = \left[ \frac{(test\ \text{value}-control\ \text{value})}{(cut-off\ (10\ s) - control\ \text{value})} \right] \times 100. \] 
Therefore, the presence of hyperalgesia will result in a decreased latency of tail withdrawal.

*Evaluation of Allodynia: von Frey Filaments*

Mechanical allodynia was assessed using von Frey filaments as previously described (Kim *et al.*, 1992; Chaplan *et al.*, 1994) with modifications. The assessment was preformed once prior to injury, and once a week following SCI until the termination of the study. The animals were placed on an elevated metal mesh floor, covered with a transparent plastic box, and allowed to habituate for 5 minutes. A single trial consisted of 5 applications of a von Frey filament (Stoelting, Wood Dale, IL) to the plantar surface using the up-down method (Chaplan *et al.*, 1994) of the hind paw with 5 seconds between applications. Filaments were applied in order of increasing force until at least 3 of the 5 applications resulted in a positive response. The 50% withdrawal threshold was modified based on the formula given by Dixon (Dixon, 1980) in which 
\[ 50\% \ \text{threshold} = X + kd, \]
where \( X \) is the value (in log units) of the final von Frey filament used, \( k \) is the tabular value for the pattern of positive/negative responses (# of positive responses/total # responses), and \( d \) is the mean difference between stimuli in log units (0.23 in this study). Positive responses were defined as withdrawal of the paw anytime throughout filament application or withdrawal. Following three paw withdrawals with a given filament size,
the previous smaller filament was repeated to confirm its negative response, and then the positive response was also repeated for confirmation.

_Evaluation of Psychological Health_

Depression was evaluated prior to the initiation of any intervention (on post-SCI day 30) and after completion of therapy (on post-SCI day 60) by using the Porsolt forced swim test (Porsolt _et al_, 1977). Administration of antidepressants has been shown to reduce the immobility time in the Porsolt test, and this test is frequently used as a screen for anti-depressant properties of compounds. We preliminarily evaluated the performance of paraplegic rats and found that rats were able to adequately perform these tests. The animals were placed in an acrylic cylindrical tank 10” in diameter, filled to a depth of 12” with water at a temperature of 30°C. Each 5 minute evaluation was preceded by a 15 min acclimation session in order to establish a “learned helplessness” in the animal. While the animal was being acclimated and tested, the observer remained out of sight from the animal so not to affect the animal’s behavior, while monitoring the animal for signs of distress through a windowed adjacent room. Both the pretreatment assessment (Day 30) and the post-treatment assessment (Day 60) were filmed and later evaluated by an evaluator naïve to treatment.

_Statistical Analysis_
Data were analyzed using SigmaStat Advisory Statistical Software v3.5 (Systat, San Jose, CA) on a personal computer with significance set at alpha < 0.05. All data are presented as mean ± SEM. To assess main effects of intervention across days, data for were analyzed using one-way ANOVAs on each day followed by a Holm-Sidak \textit{post hoc} analysis. To evaluate the main and interaction effect of the intervention across days, data were analyzed using a two-way ANOVA followed by a Holm-Sidak \textit{post hoc} analysis with the main effect of injury presented in the figures.

Results

\textit{Injury Severity and Animal Health}

The impact forces measured by the force transducer of the IH impactor were recorded immediately following injury (Figure 1A). The forces delivered to each of the four groups were not found to be significantly different. These data suggest that rats in all intervention groups received the same severity of injury. Also, the body weight of the animals was recorded daily for the duration of the experiment as an indicator of overall health. As shown in Figure 1B, at no point during the 60 day trial was there a significant difference between average body weight of treatment groups, suggesting that all animals remained healthy.
Figure 1. Injury severity and body weight of each treatment group. (A) The animals were injured with 250 kDyns of force using the Infinite Horizons impactor. The actual force delivered was recorded and averages of each group are shown with no significant differences. (B) Throughout the study the body weights were recorded daily as an indicator of overall health. Averages of each group are shown, with no significant differences.
**Functional Recovery**

The BBB open-field locomotor test was used to evaluate hind limb locomotor function following experimental SCI as previously described (Basso *et al.*, 1995; Kachadoro *et al.*, 2010). As seen in Figure 2, animals in all groups improved across days (main effect of day $F=953.3$, $p<0.001$). Animals in the control group reach a BBB score of less than 8, which corresponds to extensive movement of all three joints of the hind limb. Animals that received REHAB intervention reached scores of 8-9, which corresponds to weight supported plantar placement of the hind paws. When compared to the control group, animals in the REHAB group exhibited a consistent trend toward improved hind limb function when compared to the CTRL group that reached statistical significance ($p=0.008$) significance on day 59 (CTRL: $8.21\pm0.4$; REHAB: $9.31\pm0.27$). Neither the VEN nor VEN/REHAB groups demonstrated a statistically significant difference in hind limb function when compared to control at any point during the study (Figure 2B-C). Taken together, these data suggest that delayed post-SCI administration of REHAB confers a modest improvement in functional recovery, but that combining VEN with REHAB ameliorates the beneficial effects of REHAB on functional recovery as measured in the open field.
Figure 2. Effect of Post-SCI administration of venlafaxine (VEN) and rehabilitation (REHAB) on the Basso, Beattie, Bresnahan (BBB) score. Hind limb locomotor function was assessed by two raters naïve to treatment of the animal. Mean scores ± SEM for post-SCI days 10, 17, 24, 31, 38, 45, 52, and 59 are shown for animals receiving REHAB (A) VEN (B), or both (VEN/REHAB) (C) compared to control (CTRL). Figure 2D compares the BBB scores from all four groups. *Significantly different than CTRL on that day. n=16 for VEN and VEN/REHAB, n=15 for REHAB and CTRL.
Figure 3. Effect of post-SCI administration of venlafaxine (VEN) and rehabilitation (REHAB) on functional recovery measured using the CatWalk kinematic analysis. Results are reported as the regularity index, which is a percentage of steps that are coordinated. Mean scores ± SEM for post-SCI days 9, 16, 23, 30, 37, 44, 51, and 58 are shown for animals receiving REHAB (A), VEN (B), or both (VEN/REHAB) (C) compared to control (CTRL). Figure 3D compares the regularity index of all four groups. *Significantly different than CTRL on that day. n=16 for VEN and VEN/REHAB, n=15 for REHAB and CTRL.
One parameter of the kinematic analysis by the CatWalk system that is often reported as an indicator of functional recovery following SCI is the regularity index. The regularity index is an indicator of forelimb-hind limb coordination that represents the percentage of regular step patterns without missteps. As shown in Figure 3A, comparison of the regularity index of the REHAB and CTRL groups indicates a trend towards improved coordination of steps in the REHAB group over CTRL. This improvement seen in the REHAB group reaches statistical significance by day 58 (p=0.002). The animals that received VEN only did not show any change in coordination when compared to CTRL (Figure 3B). The group that underwent the rehabilitation while concurrently receiving VEN (VEN/REHAB) showed a modest trend towards improvement in regularity index over CTRL (Figure 3C) that did not reach statistical significance on any day evaluated. Together, these data suggest that post-SCI administration of REHAB in the chronic setting infers an improvement in functional recovery, yet administering VEN with REHAB decreases the beneficial effects of REHAB on functional recovery as measured by the regularity index in the CatWalk gait analysis.

The functional recovery of each treatment group also was assessed weekly using the Louisville Swim Scale as previously described (Smith, 2006). As seen in Figure 4, a two-way ANOVA demonstrated a main effect of group (F=16.8, p<0.001) and day (F=705.8, p<0.001). When data for each day were examined by one-way ANOVA, it was determined that administration of the REHAB therapy produced a trend toward improvement when compared to the CTRL group but this trend failed to reach statistical significance on any single day. Similarly, both groups receiving REHAB therapy showed
a trend of increased functional recovery when compared to CTRL by the final measurement on day 50, shown in Figure 4A-B (REHAB: 4.88±0.62; VEN/REHAB: 5.00±0.66; CTRL: 3.64±0.54). However, this trend failed to reach significance by one-way ANOVA on any single day. Figure 4C shows the group that received VEN only showed no change in scores over CTRL (VEN: 3.56±0.61). Altogether, it is suggested by these data that there is improvement in functional recovery following SCI in groups receiving REHAB that is not seen in the other groups.

Neuropathic Pain

The effects of VEN and REHAB interventions on thermal hyperalgesia were assessed using the tail-flick device as previously described (Dewey et al., 1970). As seen in Figure 5A, VEN group showed no significant differences in latency of withdrawal from the heat source over the CTRL group. However, the groups exposed to REHAB and the combination of VEN/REHAB demonstrated significantly less hyperalgesia when compared to CTRL, with significantly different days indicated by asterisks in Figure 5B and 5C. However, this trend of improvement in pain threshold over CTRL overall was less in the REHAB group, with the REHAB group only reaching significance over CTRL on the final assessment. These data suggest that there is an effect of decreased pain responses in groups receiving REHAB, and this effect may be amplified by concurrent VEN administration.
Figure 4. Effect of post-SCI administration of venlafaxine (VEN) and rehabilitation (REHAB) on functional recovery measured with the Louisville Swim Scale (LSS). Results were recorded by a single observer naïve to treatment. Mean scores ± SEM for post-SCI days 9, 16, 23, 30, 37, 44, 51, and 58 are shown for animals receiving REHAB (A), VEN (B), or both (VEN/REHAB) (C) compared to control (CTRL). Figure 4D compares the LSS of all four groups. #Significantly different group effect when compared to CTRL. *Significantly different group effect when compared to VEN. n=16 for VEN and VEN/REHAB, n=15 for REHAB and CTRL.
Treatment effects on mechanical allodynia were studied using von Frey filaments as previously described (Kim et al., 1992; Chaplan et al., 1994). The data demonstrating allodynia in each group are reported in Figure 6 as 50 percent paw withdrawal threshold (PWT) from the pre-injury baseline. Figure 6A shows the allodynic responses of the VEN group compared to CTRL, of which there were no differences demonstrated. As seen in Figure 6B, the REHAB group demonstrated a trend towards higher withdrawal thresholds compared to the CTRL group, reaching statistical significance only on post-SCI day 39. Lastly, Figure 6C shows that the VEN/REHAB group displayed no significant differences in allodynia over CTRL. These data, when taken together, suggest there may be a trend of increased pain thresholds, or decreased allodynia, in the animals receiving REHAB as an intervention, and there seems to be no effect of VEN on allodynic behavior. However, these were only trends as they failed to reach statistical significance.

Incidence of Priapism

Presence or absence of priapism was recorded twice a day for the duration of the study. There were no significant differences in the average number of days prior to intervention in which priapism was present between any of the four groups. The average incidence of priapism during the 30 days preceding treatment of all groups was 1.29 days, as indicated by the horizontal line in Figure 7. The bar graphs indicate the average number of days in which priapism was present in each group during intervention (post-SCI days 31-60) and prior to intervention (post-SCI day 1-31). There was significantly
Figure 5. Effect of post-SCI administration of venlafaxine (VEN) and rehabilitation (REHAB) on hyperalgesia. Mean percent maximal possible effect (MPE) ± SEM for post-SCI days 7, 14, 21, 28, 35, 42, 49, and 56 are shown for animals receiving VEN (A), REHAB (B), or both (VEN/REHAB) (C) compared to control (CTRL). Figure 5D compares the %MPE of all four groups. *Significantly different when compared to CTRL on that day. n=16 for VEN and VEN/REHAB, n=15 for REHAB and CTRL.
higher incidence of priapism in the VEN and the VEN/REHAB groups during intervention when compared to the incidence of the same group during the 30 days prior to intervention. For the groups that did not receive VEN during the intervention period (CTRL and REHAB), there was not a significant increase in incidence of priapism observed. These data suggest that venlafaxine may cause an increase in the incidence of priapism in a SCI population.

*Depression: Porsolt Forced Swim Test*

We used the Porsolt forced swim test to measure depressive behavior in the animals as previously described (Porsolt *et al*, 1977). Depression was assessed at two time points during the study; once prior to intervention on post-SCI day 30, and again at the end of the study on post-SCI day 60. One marker of depression in the test was the percentage of time spent in the water tank in an immobile state, rather than actively trying to escape. A second indicator was the time until the animal first shows signs of helplessness. The average percentage of time spent immobile and average time to helplessness (TTH) of each group on post-SCI day 60 is shown in Figure 8A-B. There were no significant differences in either immobility times or TTH between any of the groups prior to intervention, and the total average across all groups is indicated by the horizontal line in each graph. Neither measure of depression demonstrated a significant difference between groups, and there were no differences in scores prior to intervention. These data show that neither intervention affected the depressive behaviors that
Figure 6. Effect of post-SCI administration of venlafaxine (VEN) and rehabilitation (REHAB) on allodynia. Mean 50% paw withdrawal thresholds (PWT) ± SEM for post-SCI days 25, 32, 39, 46, 53, and 60 are shown for animals receiving VEN (A), REHAB (B), or both (VEN/REHAB) (C) compared to control (CTRL). Figure 6D compares 50% PWT of all four groups. *Significantly different than CTRL on that day. n=16 for VEN and VEN/REHAB, n=15 for REHAB and CTRL.
are measured by this test, which brings into question the efficacy of these therapies on depression following SCI.

Discussion

Depression has a higher prevalence in the SCI patient population than what is seen in the general population, so it is not surprising that these patients are commonly prescribed antidepressants by their physicians. However, SCI patients have altered CNS neurochemistry below the level of their lesion that may cause antidepressants to have unique side-effects which are not seen in uninjured patients. Consequently, it is important to understand the effects of antidepressants on the outcomes and complications following SCI which are mediated by the very neurotransmitters targeted by antidepressants, including functional recovery, neuropathic pain, and sexual function. Not only are the side-effects of antidepressant therapy in this patient population poorly understood, but the efficacy of these drugs on depression has not been previously evaluated in SCI patients. Additionally, physical therapy following SCI is known to help patients recover function through plasticity of the CNS. Since many SCI patients are on antidepressants while undergoing physical rehabilitation, we wished to investigate the effects these drugs have on the functional gains resulting from rehabilitation.
Figure 7. Effect of post-SCI administration of venlafaxine (VEN) and rehabilitation (REHAB) on the incidence of priapism. Presence or absence of priapism was recorded twice daily, AM and PM. Mean number of days with at least one observation of priapism ± SEM are shown for animals receiving VEN, REHAB, both (VEN/REHAB) and control (CTRL). Animals began interventions on post-SCI day 31 and the study ended on post-SCI day 60. No interventions were performed on post-SCI days 1-30. #Significant increase in the incidence of priapism resulting from intervention. n=16 for VEN and VEN/REHAB, n=15 for REHAB and CTRL.

Using BBB, LSS, and CatWalk gait analysis as measures of functional recovery, we observed significantly increased functional outcomes in the REHAB group when compared to CTRL in each assessment. These significant gains of function resulting from REHAB seen in the BBB open-field test and CatWalk gait analysis were lost in
groups co-administered VEN + REHAB. However, there were no differences observed between the VEN and CTRL groups in any of the tests. Taken together, these data suggest that the antidepressant had a deleterious effect on the functional gains resulting from rehabilitation, but did not have any effect on the baseline functional levels. This effect of VEN to ameliorate the gains seen following REHAB was not seen in the LSS, which is the least sensitive of the three measurements and may not reveal subtle differences between groups. Although the effect of VEN in reducing the functional gains conferred by REHAB was subtle with regard to some outcomes, it is an effect that merits future study and potential considerations of clinicians when developing a treatment plan for a SCI patient.

Neuropathic pain is a frequent complaint following SCI, so we investigated the effects of antidepressants on this complication. We utilized two assessments of neuropathic pain in our animal SCI models, the tail-flick test to observe hyperalgesia, and von Frey filaments to measure allodynia as previously described (Kim et al., 1992; Chaplan et al., 1994; Dewey et al., 1970). The von Frey data demonstrated trends toward decreased alldynia the group that received REHAB, although these trends only reached significance over CTRL on day 39. The tail-flick assessment shows us that the groups which received REHAB alone and VEN/REHAB in combination exhibited less hyperalgesia than CTRL. These data suggest the REHAB likely induces alterations in the spinal cord circuitry which lessen the development of neuropathic pain and that co-administration of VEN does not alter pain or the REHAB-induced reduction in neuropathic pain.
Figure 8. Effect of post-SCI administration of venlafaxine (VEN) and rehabilitation (REHAB) on depressive behavior assessed using the Porsolt forced swim test. The animals spent 5 minutes in the swim tank, and time spent immobile and the time until first sign of helplessness (TTH) were recorded. Mean times ± SEM for shown for the assessment performed at the completion of the study (post-SCI day 60). Horizontal line indicates average of all groups for pre-intervention assessment (post-SCI day 30). There were no significant differences between groups in either assessment for both time spent immobile (A) and TTH (B). n=16 for VEN and VEN/REHAB, n=15 for REHAB and CTRL.
Depressive behaviors were also assessed in each treatment group using the Porsolt forced swim test as previously described (Porsolt et al, 1977). The animals were assessed once prior to intervention and again at the completion of the study to assess the effects of REHAB and VEN on depression. Depression was assessed by using two measurements, percentage of time spent in an immobile state and the amount to time to first immobile state. Both outcomes failed to produce any significant differences between groups, suggesting that both VEN and REHAB fail to alleviate depression in a SCI animal. However, this needs to be further evaluated using alternate depression behavioral assessments, as this test was developed for non-injured animals. SCI animals demonstrate unique behaviors while swimming due to their impaired function when compared to non-injured animals. For example, non-injured animals have more abdominal and tail strength, making it easier to assume an immobile posture comfortably. We found that when a highly impaired injured animal assumes an immobile posture, the animal will sink below the water level more rapidly than a non-injured animal, which provides more motivation to resume an active state in order for the animal to keep its head above water. Even though this is a possible confounder, we did not observe any significant differences in immobility times in the very group that did demonstrate significant improvements in functional recovery.

Sexual dysfunction is a common concern in this patient population. In our study, we observed a significant and substantial increase in the incidence of priapism in both groups receiving VEN when compared to the occurrence prior to injury, while the CRTL and REHAB groups exhibited no significant differences during the 30 days of intervention when compared to the incidence prior to onset of the intervention. We
hypothesize that this finding is the result of norepinephrine (NE) reuptake inhibition on the sympathetic innervations of the penile tissues. Erections are mediated by autonomic nerve inputs, where the parasympathetic meditates erection while the sympathetic portion controls remission of erection. Following SCI, both autonomic inputs are impaired as are all innervations below the level of lesion. Blocking reuptake of NE will therefore impair the recycling of the neurotransmitter ubiquitously in the nervous system; however this impairment has much more significant implications in an injured patient than a non-injured patient. In the injured patient, transport of NE originating in the brainstem is severely impaired and reuptake blockade results in the inability for the neurons below the level of lesion to recycle the scarce neurotransmitters that are not synthesized in the spinal cord. The effect is a tipping of the balance in the penile tissue to favor parasympathetic input, resulting in an irremissible erection. This is not mechanism unique to SCI patients, as it is documented that cocaine, a NE reuptake inhibitor, when abused chronically can lead to priapism in non-injured patients (Munarriz et al, 2003). Also, priapism it is an established side effect of the atypical antidepressant trazodone, which has NE antagonistic properties (Rosenberg et al, 2009; Sood et al, 2008). Interestingly, there is a case report of priapism in a cervical SCI patient that may have been due to NE reuptake inhibition. The case study centered on a patient who was suffering from priapism, for which they were able to manage with a prescription of baclofen in addition to the patient’s many other medications, one of which was Mianserin, an antidepressant with NE reuptake inhibition characteristics (Vaidyanathan, 2004). Perhaps a better alternative for such a patient, given our findings, would be to first
try an alternative antidepressant therapy prior to adding an additional drug to treat what could be simply an untoward effect of the primary medication.

In summary, this study was the first to systematically evaluate the effect of post-SCI administration of an antidepressant on functional recovery with and without rehabilitation in an animal model of SCI. Although more research should be done to address this issue, our data suggest that combining VEN with REHAB negates the benefits of REHAB. Clearly, this issue should be addressed further with regard to the temporal window, dose, and underlying mechanisms, but our data indicate that caution and rigorous evaluation should be employed in the clinical management of persons with SCI and depression.
References


OVERALL CONCLUSIONS

The goal of this project was to employ a SCI rodent model to assess the effect of venlafaxine administration on functional recovery. Epidemiological data indicate that the rate of depression in SCI patients is higher than the general population, with estimates as high as 37% (Saunders et al., 2011). Typically, clinicians compassionately strive to treat depression in persons with SCI typically by prescribing antidepressants, even though the effects of these medications in persons with SCI have not been thoroughly evaluated. This is concerning, especially since antidepressant medications alter central nervous system (CNS) neurochemistry, including serotonergic and adrenergic signaling, both critical regulators of plasticity and functional recovery after SCI. It will be relevant for clinicians to have a full understanding of what effects these drugs may have on functional recovery, as well as the other complications mentioned, in order to make a well informed decision on what therapeutic modalities to prescribe to SCI patients in the chronic setting. This study was the first attempt to systematically evaluate the effects of antidepressants in the SCI, and a clinically-relevant animal model was employed.

The first result from this study is the effect venlafaxine (VEN) has on functional recovery in the rehabilitation (REHAB) setting following SCI. The data suggest that VEN does not alter the baseline functional levels, but may decrease the gains seen as a result from REHAB. This is an alarming finding, due to the prevalence of depression in this patient population. These data suggest that an SCI patient prescribed antidepressant
medication while undergoing REHAB may experience decreased functional gains when compared to patients in REHAB who are not also taking antidepressants. This novel finding needs to be further investigated in other rodent models and in human patients in order to ensure physicians have the knowledge required to maximize recovery from SCI.

A second finding which is highly clinically relevant is the data assessing the alleviation of neuropathic pain with antidepressant therapy. We found that the animals receiving VEN experienced a significant group effect in the reduction of hyperalgesia, but the reduction in allodynia was non-significant. Taken together, this effect of VEN on neuropathic pain was less than overt. Although pain is a common complaint following SCI and should be addressed, these data suggest that perhaps VEN is not an optimal therapy for this complaint due to the effects on functional recovery we observed. Finding another therapy with greater efficacy minus the effects on function should be chosen as a potential treatment for neuropathic pain instead.

Thirdly, we investigated the efficacy of VEN on depression in a rodent SCI model, which is the first time an antidepressant have been evaluated for efficacy in reducing depression in a SCI model. Our data obtained using the Porsolt forced-swim test, suggest that VEN has no effect on the depressive behaviors in a SCI model. This is a very interesting finding that needs to be confirmed using alternate depression tests. If antidepressants indeed have reduced efficacy on depression in this population, this finding would potentially raise concerns about the use of this class of antidepressants when planning care for a SCI patient. However, the Porsolt test was designed for non-injured animals and this was the first time it was used in an animal model with impaired function. These findings need to be confirmed with a test in which variable motor
function is not a possible confounder as well as evaluated in other models of SCI and potentially in clinical trials.

Lastly, our study showed an impressive and significant increase in the incidence of priapism in the groups receiving VEN as an intervention. This is a novel side-effect for this drug, although other drugs that also block reuptake of norepinephrine, such as cocaine, have been reported to cause priapism (Munarriz et al, 2003). This is an important result pertaining to SCI patients, as priapism provides an objective, physiological finding that allows for the observation of an antidepressant altering neurochemistry. This is strong evidence that antidepressants are not the benign drugs as once thought in the medical and lay communities, and can have unexpected distant end-organ untoward effects.
GENERAL LIST OF REFERENCES


NOTICE OF RENEWAL

DATE: May 24, 2012

TO: CANDACE L. FLOYD, Ph.D.
SRC: 547 7330
FAX: (205) 934-5086

FROM: Judith A. Kapp, Ph.D., Chair
Institutional Animal Care and Use Committee (IACUC)

SUBJECT: Title: Effect of Amidepresant Therapy on Psychological Health, Rehabilitation, Plasticity and Functional Recovery in a Rodent Model
Sponsor: Department of Defense
Animal Project Number: 120609180

As of June 23, 2012, the animal use proposed in the above referenced application is renewed. The University of Alabama at Birmingham Institutional Animal Care and Use Committee (IACUC) approves the use of the following species and numbers of animals:

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<th>Use Category</th>
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<td>Rats</td>
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Animal use must be renewed by June 22, 2013. Approval from the IACUC must be obtained before implementing any changes or modifications in the approved animal use.

Please keep this record for your files, and forward the attached letter to the appropriate granting agency.

Refer to Animal Protocol Number (APN) 120609180 when ordering animals or in any correspondence with the IACUC or Animal Resources Program (ARP) offices regarding this study. If you have concerns or questions regarding this notice, please call the IACUC office at (205) 934-7602.
NOTICE OF RENEWAL

DATE: April 6, 2012
TO: CANDACE L. FLOYD, Ph.D.
SRC -547 7330
FAX: (205) 934-5086

FROM: Judith A. Kapp, Ph.D., Chair
Institutional Animal Care and Use Committee (IACUC)

SUBJECT: Title: Effect of fluoxetine treatment on exercise rehabilitation in SCI
Sponsor: Internal
Animal Project Number: 120509130

As of May 27, 2012, the animal use proposed in the above referenced application is renewed. The University of Alabama at Birmingham Institutional Animal Care and Use Committee (IACUC) approves the use of the following species and numbers of animals:

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Animal use must be renewed by May 26, 2013. Approval from the IACUC must be obtained before implementing any changes or modifications in the approved animal use.

Please keep this record for your files, and forward the attached letter to the appropriate granting agency.

Refer to Animal Protocol Number (APN) 120509130 when ordering animals or in any correspondence with the IACUC or Animal Resources Program (ARP) offices regarding this study. If you have concerns or questions regarding this notice, please call the IACUC office at (205) 934-7992.