Research article

A randomized controlled trial of venlafaxine XR for major depressive disorder after spinal cord injury: Methods and lessons learned

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Context/objective: We describe the rationale, design, methods, and lessons learned conducting a treatment trial for major depressive disorder (MDD) or dysthymia in people with spinal cord injury (SCI).

Design: A multi-site, double-blind, randomized (1:1) placebo controlled trial of venlafaxine XR for MDD or dysthymia. Subjects were block randomized and stratified by site, lifetime history of substance dependence, and prior history of MDD.

Setting: Six SCI centers throughout the United States.

Participants: Across participating centers, 2536 subjects were screened and 133 were enrolled into the trial. Subjects were 18–64 years old and at least 1 month post-SCI.

Interventions: Twelve-week trial of venlafaxine XR versus placebo using a flexible titration schedule.

Outcome measures: The primary outcome was improvement in depression severity at 12 weeks. The secondary outcome was improvement in pain.

Results: This article includes study methods, modifications prompted by a formative review process, preliminary data on the study sample and lessons learned. We describe common methodological and operational challenges conducting multi-site trials and how we addressed them. Challenges included study organization and decision making, staff training, obtaining human subjects approval, standardization of measurement and treatment, data and safety monitoring, subject screening and recruitment, unblinding and continuity of care, database management, and data analysis.

Conclusions: The methodological and operational challenges we faced and the lessons we learned may provide useful information for researchers who aim to conduct clinical trials, especially in the area of medical treatment of depression in people with SCI.

Keywords: Antidepressants, Dysthymia, Major depressive disorder, Pain, Randomized controlled trials, Research design, Spinal cord injuries

Introduction

Major depressive disorder (MDD) and other depressive syndromes are common and disabling among people with spinal cord injury (SCI).^{1–3} The prevalence of

MDD during inpatient rehabilitation is between 20–43% and 25–30% among those residing in the community.⁴ Depressive symptoms are related to the development of pressure sores and urinary tract infections,⁵ poorer self-appraised health,⁶ community mobility and social integration and less leisure activity,⁷ fewer meaningful social pursuits,^{8,9} greater unemployment,¹⁰ and higher all cause mortality.¹¹

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Despite the prevalence and negative impact of depression after SCI, high-quality depression treatment trials in this population are virtually nonexistent.¹² Antidepressant studies in SCI are limited to simple open trials of various medications (mostly tricyclic antidepressants), all of which tended to claim benefit.^{13–16} Trials examining the effectiveness of non-drug interventions are equally limited. Randomized controlled trials (RCTs) of coping effectiveness training,¹⁷ exercise,¹⁸ and massage¹⁹ that examined depression as an outcome did not select persons with MDD. Non-randomized trials of psychological interventions also have treated heterogeneous samples rather than people with MDD.^{20–22} The single published trial designed to treat MDD after SCI was non-randomized.¹² People with SCI and MDD who accepted a course of cognitive behavior therapy (CBT) were compared to those who refused CBT.¹²

The need for more rigorous research in this area, especially clinical trials, has been documented in multiple literature reviews.^{1,23,24} Experts have concluded that it is neither scientifically valid nor clinically prudent to assume that antidepressant medications are effective in people with SCI.^{1,2,23} The absence of definitive studies that demonstrate effectiveness may also underlie current depression prescription practices, which are characterized by under-treatment. A recent survey of 947 community-residing people with SCI found that only 29% of those with probable MDD received any antidepressant, 16% received a guideline level dose, and 11% received a guideline level dose and duration.²⁵ As we will describe below, it no longer seems tenable to rely on a clinical practice guideline solely based on evidence from studies of persons without spinal injury.⁴ The lack of RCTs in this area can be attributed to several factors including high cost, methodological difficulties associated with implementing such trials, and lack of adequate resources (i.e. investigators training, and patient unavailability or low motivation to enter such trials).

The purpose of this article is to describe the methods adopted when planning and implementing a multi-site RCT designed to treat major depression disorder in persons with SCI. This trial was approved as one of two spinal cord injury model systems (SCIMS) collaborative projects funded by the National Institute on Disability and Rehabilitation Research (NIDRR), U.S. Department of Education (Grant # H133A 060107). The original study sites consisted of the University of Washington, Seattle (lead center), University of Michigan, Ann Arbor, Northwestern University/Rehabilitation Institute of Chicago, and the University of Alabama, Birmingham. During the trial we added

Baylor Institute for Rehabilitation (BIR), Dallas and the University of Miami, Miami. Grant support was approximately \$900,000 per year for the calendar years 2007–2011. Two successive no-cost extension years (2012–2013) were permitted by NIDRR to complete the work. The trial was named the Project to Improve Symptoms and Mood after Spinal cord Injury (PRISMS). This article serves as a methodological reference for the subsequent outcome papers that derive from this trial. This paper also discusses major issues and concerns related to multi-site trial planning and execution. As such, a secondary purpose of the paper is to provide information for investigators who wish to conduct similar research in the future.

Rationale for a randomized, placebo-controlled trial to treat MDD among persons with SCI

Clinical drug trials are expensive, time consuming, labor intensive, and must be justified; especially when antidepressants are already widely used and assumed to be effective.²⁶ We justified this trial based on the benefits derived from placebo-controlled trials of antidepressants in other medical populations with high rates of co-morbid major depression. Major antidepressant trials have been conducted in coronary artery disease,²⁷ unstable ischemic heart disease,²⁸ diabetes,^{29,30} HIV/AIDS,³¹ and stroke.³² These studies provided data on antidepressant safety and efficacy and have been instrumental in establishing evidence-based guidelines for screening and treatment of depression in these populations. Whereas such guidelines are absent in the SCI population, this trial could make a significant contribution to existing rehabilitation treatment and clinical practice.

This trial was justified based on uncertainties about the efficacy and tolerability of antidepressants in SCI. Doubts about the efficacy of antidepressants in the context of SCI are based on the fact that people with SCI have comorbidities and other conditions that are associated with poor response to antidepressant medications. Persons with SCI have high rates of comorbid medical conditions³³ and the presence of medical comorbidities predicts poor response to depression treatment in chronically ill patients.³⁴ The following conditions are common among people with SCI and are associated with poor response to antidepressants: traumatic brain injury,^{35–37} chronic pain,³⁸ unemployment and impoverishment,^{39–41} and ADL dependence.⁴²

Doubts about the tolerability of antidepressants came from an influential case study that reported selective-serotonin reuptake inhibitors (SSRIs) contributed to increased spasticity in people with SCI.⁴³ The

prevalence of this potential side effect is unknown, but the cause is likely due to denervation super sensitivity or serotonin syndrome.⁴⁴ In addition, two-thirds of veterans with SCI diagnosed with depression and treated with SSRIs did not continue antidepressant treatment for the recommended 6-month period.⁴⁵ The reasons veterans discontinued early were not identified, but antidepressant side effects may be less tolerable in people with SCI especially when combined with other medications that have similar side effects.

We concluded that there was clinical equipoise regarding the efficacy of pharmacotherapy to treat MDD in people with SCI and that a randomized placebo-controlled trial was indicated. Justification for a placebo-controlled trial was based on the absence of level I evidence for any form of depression treatment in people with SCI. Moreover, a placebo arm was deemed necessary due to the heterogeneity of patients and the uncertain, often fluctuating course of depression following SCI. A double-blind placebo condition controls for non-specific factors, such as therapeutic relationship, enthusiasm, and patient and physician expectations, as well as natural improvement, and regression to the mean of outcome measures. Furthermore, use of placebo controls allows investigators to assess the prevalence of adverse effects beyond those attributed to the inert placebo (the so-called nocebo effect), which can be highly prevalent and widely variable. This type of study meets criteria for level I evidence, the level of evidence that has the greatest potential to influence scientific thinking and clinical practice. Finally, an equivalence trial of two antidepressants is premature and would have to be so large that it would prevent adequate enrollment and timely completion of the study.

Rationale for pain as a secondary outcome of the PRISMS trial

Pain and depression are common co-occurring secondary conditions after SCI⁴⁶ and both are known to negatively impact quality of life (QOL).^{47,48} Roughly 50–70% of persons with SCI experience chronic pain and 20–30% have chronic pain that is severe.^{1,49,50} Those who report persistent pain exhibit more depression.^{51,52} Pain during inpatient rehabilitation predicts the development of depression during inpatient rehabilitation⁵³ as well as depressed mood 2 years after SCI.⁵⁴ The relationship between depression and pain is likely bi-directional.⁵³

Antidepressants have been studied as a treatment for pain after SCI. Amitriptyline, a tricyclic antidepressant was not effective for SCI-related pain in one RCT,⁵⁵ but in another trial was effective for SCI-related neuropathic pain in people who were also depressed.⁵⁶ However, in both studies, side effects may have limited dose

escalation and triggered dropouts.^{55,56} The analgesic effect of tricyclics is probably due to blocking the reuptake of the neurotransmitter norepinephrine.⁵⁷ Therefore, newer serotonin–norepinephrine reuptake inhibitor (SNRI) antidepressants such as venlafaxine XR, which have a more favorable side-effect profile, are promising medications for SCI-related pain, especially the neuropathic type. The need for better treatments for neuropathic pain as well as recent pharmaceutical advances prompted the investigators to plan this trial to also test the efficacy of venlafaxine XR to treat pain after SCI.

Rationale for venlafaxine XR

We considered the entire range of antidepressant agents and decided on venlafaxine XR (Effexor XR[®] extended release; Pfizer Inc., New York, NY) because of several important potential advantages for its use in persons with SCI. Venlafaxine XR is similar to some tricyclic antidepressants (e.g. nortriptyline and amitriptyline) in that it is a combined SNRI. However, venlafaxine XR has lower rates of potential adverse effects commonly found in tricyclics, such as anticholinergic and antihistaminic effects, sedation, cognitive dysfunction, orthostatic hypotension, and electrocardiogram changes.^{58,59} Venlafaxine XR is also safer in overdose than other commonly used antidepressants, including tricyclics, and has low potential for drug interactions.^{58,59}

Venlafaxine is as effective and perhaps even more effective than other antidepressant medications.⁶⁰ A meta-analysis of eight studies showed venlafaxine to be superior to SSRIs in terms of the percent of people who responded to treatment, the percent that experienced complete remission of depression and how quickly the medicine began to have a positive effect (as early as 4 days).⁶¹ The extended release venlafaxine (XR) permits once daily dosing and is as effective as the original immediate-release formulation.^{58,59,62,63} The therapeutic effects of venlafaxine do not appear to diminish over time, as compared with SSRIs.⁶⁴

As noted above venlafaxine also may be advantageous in the SCI population because of its analgesic potential. Case series and animal studies have shown that venlafaxine, by virtue of its norepinephrine reuptake inhibition or opiate mediation, may be effective in treating a variety of pain syndromes, including neuropathic pain.^{57,65–69}

Designing and implementing the PRISMS trial: a review of methods

Overview

The grant was awarded in October 2006. The start date was pushed back from 1 November 2006 to 1 January

2007 to allow more time for preparatory work. Subject enrollment began in July 2007 and in August 2007 the funding agency initiated a formative review of the grant. Outside experts (Drs Andrew Nierenberg and Sejong Bae) reviewed the grant proposal and along with NIDRR representatives (Drs Theresa San Agustin and William Schutz) met with the study investigators on 11 October 2007 to present recommendations and discuss suggested modifications to the study design and assessment plan. Many of the lessons learned and design changes emerged from this review.

Study hypotheses

We considered the strengths and weaknesses of alternative primary study hypotheses. One option was to compare the 12-week response rates on the primary outcome measure in the venlafaxine XR versus placebo control groups. The response rate is the proportion of each group that has at least a 50% decrease in depression severity on the primary outcome measure from baseline to the end of treatment. Response rate has a well-established history in psychiatric treatment literature as an indicator of clinically significant change.⁷⁰ However, response rate is also statistically conservative as it is a binary outcome based on only two points in time. The other option was to treat the primary outcome as a continuous measure and use data from all interim visits. This approach offers greater statistical power, but results are not anchored to clinically significant change. The more conservative analytic approach was written into the proposal because it was expected that grant reviewers would have greater familiarity with and enthusiasm for a study designed to achieve a broadly recognized measure of clinically meaningful change.

Our secondary hypotheses related to the potential impact of venlafaxine XR on self-reported pain intensity and pain interference (especially among those with neuropathic pain), community participation, health-related QOL, and satisfaction with life. Tertiary hypotheses predicted that those with a lifetime history of substance dependence⁷¹ and those with no prior history of MDD²⁸ would demonstrate a significantly lower response to treatment compared with those without these factors. Finally, we planned to reassess depression severity in all treatment responders at 24 weeks. We predicted that venlafaxine XR responders would demonstrate lower relapse rates compared to placebo responders.

Selecting PRISMS outcome measures

We chose the 17-item Hamilton Depression Scale (HAM-D) as our primary outcome measure largely

because of its longstanding, widespread reputation as the gold-standard measure of depression severity for depression treatment trials. Moreover, the HAM-D has established benchmarks for clinically significant treatment response (at least a 50% decrease in the total score) and remission (a score less than 8).^{72,73} Nevertheless, the HAM-D has been criticized for being multifactorial and insensitive to change due to the many somatic symptoms that may not improve, especially in subjects with significant medical comorbidity.⁷⁴ Therefore, during the formative review the consultants suggested that we consider using one of several unidimensional subscales of the HAM-D such as the Maier or Bech.^{75–77} They advised us to monitor emerging research on these subscales because one or more may prove to be more sensitive to change than the 17-item version.^{78–80} By the end of the trial, evidence was still lacking that these subscales were more sensitive to change than the original 17-item version and no relevant studies had been done in SCI. Therefore, we retained the 17-item version as our primary outcome measure and planned to conduct a *post hoc* analysis of our data to identify the depression outcome measures with the best psychometric properties.

Other outcome measures were chosen based on having solid psychometrics, including sensitivity and proven utility in or relevance to individuals with SCI. Study measures were completed at fixed time-points (see Table 1) and administered in interview format to facilitate consistency and data completeness.

Project design and phases

The project was designed to have two phases: a screening phase and a treatment phase (Fig. 1). We anticipated that a large number of people would need to be screened in order to enroll a sufficient sample (about 10:1) and that this represented an opportunity to conduct focused survey research. Therefore, the screening phase always contained a core set of questions about inclusion and exclusion criteria as well as several waves of survey research modules. These survey modules covered several study topics, some of which have been published: (1) depression treatment history,²⁵ (2) modifiable risk factors for depression,⁸¹ (3) depression and post-traumatic growth, (4) depression and community participation, and (5) the relationship between depression and positive psychology constructs such as resilience, positive affect, and spirituality.

During the start-up period the study team established the necessary administrative and operational structures at the lead center and participating sites. These preparatory steps ensured adequate communications among

Table 1 Measures

Measures	Weeks of treatment with study drug						
	Baseline						Outcome
	0	1	3	6	8	10	12
<i>Medical/somatic</i>							
SCI level and severity (ASIA Impairment Scale) ⁹⁶	X						
Charlson Medical Comorbidity Index (adapted) ⁹⁷	X						
Modified Ashworth Spasticity Scale ⁹⁸	X	X	X	X	X	X	X
MGH Antidepressant Treatment Response ⁸²	X						
Side effects checklist	X	X	X	X	X	X	X
Brief Pain Inventory ⁹⁹	X						X
<i>Psychological</i>							
Structured Clinical Interview for DSM IV (depression, dysthymia, bipolar, alcohol dependence, other drug dependence, schizophrenia, psychosis) ⁸⁶	X						X
Hamilton Rating Scale for Depression ¹⁰⁰	X	X	X	X	X	X	X
Symptom Checklist-20 depression scale ¹⁰¹	X	X	X	X	X	X	X
Patient Health Questionnaire-9 depression scale ¹⁰²							
Clinical Global Impression Scale ¹⁰³	X	X	X	X	X	X	X
Patient Global Impression of Improvement	X	X	X	X	X	X	X
Generalized Anxiety Disorder-7 ¹⁰⁴	X						X
Post-traumatic Symptom Checklist-Civilian Version ¹⁰⁵	X						X
Patient Health Questionnaire-Panic Screen ¹⁰⁶	X						X
Family History Research Diagnostic Criteria ¹⁰⁷	X						
<i>Participation, quality of life, and functioning</i>							
Craig Handicap and Reporting Technique-Short Form ¹⁰⁸	X						X
Satisfaction with Life Scale ¹⁰⁹	X						X
Sheehan Disability Scale ¹¹⁰	X						X
Medical Outcomes Study Short Form-12 ¹¹¹	X						X
<i>Environmental</i>							
Craig Hospital Inventory of Environmental Factors-Short Form ⁹²	X						
Medical Outcomes Study Social Support Survey ¹¹²	X						

MGH, Massachusetts General Hospital.

sites, standardization and uniformity of protocols, mechanisms by which to reach consensus and make decisions, metrics by which to evaluate site productivity, data sharing and safety protocols, and implementation of budgetary regulations.

Administrative issues: study organization, training, and oversight

Study organization and responsibilities

Ongoing study management was conducted via monthly committee conference calls organized by the lead center. Three committees were formed: screening, treatment trial, and steering. The screening committee dealt with case finding and recruitment up until the point of enrollment in the treatment trial. This committee monitored screening rates, recruitment rates, treatment trial accrual, and screening data entry. The treatment committee monitored participants through the treatment trial, paying particular attention to adverse events, retention rate, reliability and validity of outcome assessments, and treatment data entry. The steering committee, composed of site

principal investigators (PI), made decisions by consensus on recommendations coming from the screening or treatment committees and the lead center PIs. It developed and oversaw authorship and publication policies, study-wide budgeting decisions and strategic planning. The steering committee developed screening phase survey modules and collaborated on publications. Urgent concerns, such as questions about inclusion criteria, managing side effects, titration, subject safety concerns, and adverse events were brought directly to the Co-PIs at the lead center and handled via telephone calls or email.

Composition and training of study teams

At each site, study staff included a site PI, prescriber, back-up prescriber, unblinder, a higher level study staff person (trained to administer outcome measures and coordinate the study), and lower level study staff person responsible for screening, recruitment, and data entry. Study staff members were originally trained during a two-day meeting in Seattle. Training of the

Figure 1 Study schema.

entire group included an overview of the study rationale and procedures, with a particular emphasis on recommendations for screening, enrollment, and study safety procedures. Training included an introduction to the tracking and main databases. Next, the groups were split into prescriber and non-prescriber subgroups. The prescribers were trained in how to conduct the flexible titration protocol, including assessment of response to treatment with the Patient Health Questionnaire (PHQ)-9 as well as the assessment of side effects and spasticity. The prescribers were trained in how to conduct tapering and unblinding. Some prescriber training, such as how to unblind the sample, was conducted by telephone because prescribers were not always available for in-person training. The non-prescribers were trained in administration and scoring of screening and outcome assessment measures (see below for the process of establishing inter-rater reliability and validity). With this group, we covered use of the on-line tracking database, data entry into the statistical

database, and data-sharing procedures. When new sites were added, a team from the lead center traveled to that site to conduct the start-up training.

Inter-rater reliability of depression outcome measures

The primary outcome, depression severity, and the diagnosis of MDD were based on interviews that must be performed in a standardized fashion across sites. For the primary outcome measure we used a structured interview guide version of the HAM-D that has been shown to improve inter-rater reliability.⁸² For the diagnosis of MDD, we used the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM IV) (SCID).⁸³

We set up the following structure to achieve and maintain inter-site standardization. Each site had a primary outcome assessor and a back-up rater (a psychiatrist or psychologist). We monitored inter-rater reliability between the primary and back-up raters at each site.

We also tracked agreement between the primary rater at each site and the SCID expert rater at the lead center (CW). All raters completed the SCID training video series pertaining to MDD, dysthymia, bipolar disorder, and substance dependence. During the start-up training, the HAM-D and SCID expert rater from the lead center conducted in-person SCID and HAM-D training of all site raters. Training involved didactic presentations, demonstrations, role-plays with feedback, and coaching on how to make scoring judgments. Until each site achieved inter-rater reliability between raters and with the expert, all interviews were audio-recorded and conducted jointly by the primary rater and back-up rater. The two raters completed their scoring sheets independently followed by a consensus decision regarding SCID diagnoses and HAM-D scores. Audio-recordings as well as copies of the SCID and HAM-D scoring sheets were sent to the expert, who listened to the interviews, independently scored the SCID and HAM-D, and compared her scoring to the other two raters. She provided corrective feedback and coached the raters in interviewing technique and scoring as needed. This process was continued until each rater achieved agreement with the expert on at least 90% of the SCID items and 90% of the HAM-D items on two consecutive ratings. Similarly, the primary and back-up raters performed assessments together until they achieved 90% item-level agreement. To prevent drift, reliability between raters at each site as well as between the primary rater at each site and the expert, were rechecked annually.

IRB and regulatory issues

The lead center obtained Human Subjects Institutional Review Board (IRB) approval first and sent approved materials to the other study sites. However, IRB requirements and standards were not consistent across sites. Independent IRB review of the study protocol at all sites required considerable editing and, in one case, caused substantial delay in start-up. The formative review occurred after the initial IRB approval was obtained. The review further complicated and delayed the human subjects review process. Each of the survey modules required IRB modifications to be made at all sites. Decisions regarding protocol changes and the associated IRB modifications had to be made far in advance of when the change was to be implemented. Considerable staff time and grant funds were needed to meet and maintain IRB requirements at all sites.

Data and safety monitoring

Safety was monitored at the level of the subject, the site, and the overall study. Each site monitored the clinical

condition of all participants at a frequency and intensity that was greater than standard care. At each evaluation staff assessed depression severity, suicidal ideation, and study medication side effects. We devised protocols for defining and managing significant clinical deterioration as well as emergence of a suicidal plan or suicidal intent among enrolled participants. This included having a plan to provide continuous emergency clinical coverage by psychiatrists or psychologists at each site. The principal investigators at each site and at the lead center provided another level of back-up coverage via pager.

Each site PI was responsible for data and subject safety monitoring at their own site in accordance with institution specific IRB rules, including rules for reporting adverse effects to the IRB. Serious adverse effects were reported to the lead center and other sites.

A data and safety monitoring board (DSMB) provided external oversight over the entire study. The DSMB met once to introduce members to the study and approve a monitoring plan. The DSMB met twice more to review the results of two interim safety, efficacy, and futility analyses. The formative review consultants recommended that the DSMB should be independent from the study team, consistent with National Institutes of Health recommendations.⁸⁴ A biostatistician not affiliated with the study led the DSMB. The DSMB also included a SCI physician, ethics expert and consumer. The DSMB required a thorough examination of source documents (e.g. completed consent forms, randomization logs, prescription logs). Prior to the second meeting this review led to detection of problems with randomization procedures at one site. This revelation prompted a deeper investigation of source documents and safety implications, temporary suspension of recruitment, and a development of a remediation plan. Fortunately the investigation revealed that subject safety was not significantly impacted and that there was minimal potential for the errors to influence study efficacy. The DSMB recommended that two cases be re-examined if the results of the trial were equivocal. At both interim DSMB meetings, reviews of unblinded data including treatment efficacy and futility analyses determined that there was no reason to halt the study.

Drug randomization and distribution

The investigational drug service (IDS) at the lead center was responsible for training and coordination with the pharmacies at all sites. The biostatistician worked with the IDS to distribute randomization logs to each of the sites. The IDS received venlafaxine XR, produced the placebo, and encapsulated each into blinded study drug A and B. The IDS ensured each site had adequate

supplies of fresh study drug. Drug dispensing was done at each site by a trained pharmacist.

PRISMS phase 1: screening and recruitment

Criteria for inclusion and exclusion

The original inclusion criteria were (1) at least 18 years old; (2) SCI of any level; (3) American Spinal Injury Association Impairment Scale A–D; (4) 1–20 years post-SCI; (5) positive (≥ 10) on the PHQ-9 depression screen twice, at least 10 days apart; (6) meets DSM IV⁸⁵ criteria for MDD; and (7) reports at least moderately severe depression (≥ 17) on the HAM-D. The depression duration and severity criteria were put in place to avoid including people with transitory or mild depressive symptoms because spontaneous remission is more likely and antidepressant medications are less likely to be more efficacious than placebo for this subgroup.⁸⁶

The original exclusion criteria were (1) current suicidal ideation with intent or plan; (2) lifetime history of suicide attempt; (3) history of schizophrenia or bipolar disorder; (4) currently receiving evidence-informed treatment specifically for depression; (5) current alcohol or drug dependence (past month); (6) history of non-response to venlafaxine XR; (7) unstable dose of psychoactive medications within the past two weeks; (8) unstable medical condition within the past 2 weeks; (9) pending surgery within 3 months; (10) pregnancy; (11) breastfeeding; (12) cognitive impairment significant enough to invalidate self-reported outcomes; and (13) not fluent in English. People on unstable dosages of psychoactive medications along with those who were medically unstable were followed and rescreened once stability was achieved. Persons on low dosages of tricyclic antidepressant or trazodone for pain, sleep, or bladder dysfunction were not excluded if their dose was sub-therapeutic based on the Massachusetts General Hospital treatment response guidelines.⁸⁷ People currently on another antidepressant were considered eligible for the trial only if they had demonstrated non-response to at least 6 weeks of a minimally effective dose of that antidepressant.⁸⁷ With their consent and the concurrence of their physician, non-responders were tapered off their current ineffective antidepressant medication, underwent the baseline assessment, and if eligible, were started on the randomized study drug. While those receiving evidence-informed psychotherapy for depression were excluded, participation in supportive psychological or vocational counseling was permitted. Finally, we decided to include people as early as 1 month after SCI because MDD often begins soon after SCI and antidepressant

treatment was often initiated during this period. However, not all sites obtained permission to enroll this early.

During the formative review the consultants recommended several changes to inclusion/exclusion criteria. They thought that 20 years post-SCI was an arbitrary limit that could be dropped. However, they noted that the efficacy of antidepressants among persons 65 years and older is not well established. They recommended we restrict our age range to 18–64 years.^{88,89} They recommended that we “disaggregate” screening and outcome measures. That is, we should not use our primary outcome measure, the HAM-D, as a screening measure or study inclusion criteria. Disaggregation would circumvent the potential problem of enthusiastic screeners unconsciously inflating the baseline HAM-D score in order to recruit more people. Therefore, we adopted a higher cutoff of 12 on the PHQ-9 as an indicator of moderately severe depression *in lieu* of using the HAM-D. Later we lowered the PHQ-9 cutoff score to the standard cutoff of 10 or more as long as the subject endorsed at least one of the two cardinal symptoms (depressed mood or anhedonia). The consultants suggested we include people with dysthymia (chronic sub-clinical depression) because this diagnosis is included in many depression treatment trials and dysthymia is responsive to antidepressant treatment, including venlafaxine.⁹⁰ The consultants thought that excluding people with a single suicide attempt was overly cautious and would reduce the generalizability of the study. We agreed to include people with no more than one suicide attempt, provided the attempt was not within the past 5 years.

Recruitment of subjects into the trial: challenges and changes

We conducted case-finding for the study in clinical and community settings at all sites. In outpatient clinics and some inpatient rehabilitation units we conducted routine screening. We also asked for provider referrals, posted flyers and distributed study brochures. Non-clinical sources of subjects included people involved in SCIMS follow-up studies, other site-specific SCI databases, independent living centers, and SCI-related community organizations. We advertised the study in newsletters, flyers, webpage ads, and email lists as well as through stories and ads published in disability-related magazines. One site posted ads on busses.

Potential subjects were approached in-person by study staff in clinics and inpatient units or by telephone in response to informational flyers, advertisements, or clinician referrals. Based on ongoing discussions during the

Steering and Screening Committee meetings, we found that the most successful recruitment method was systematically approaching and screening patients in outpatient rehabilitation clinics. A small monetary incentive was offered to undergo screening. Those who consented to be screened, completed interviews consisting of the PHQ-9, key inclusion and exclusion criteria, and whatever questions were in the current survey module. We invited those who met initial screening criteria to schedule an in-person diagnostic assessment 2 weeks after the initial screening. The 2-week wait period was interposed in an effort to exclude persons with transient depressive symptoms. Those who agreed were contacted by telephone and rescreened with the PHQ-9 several days before the in-person assessment in order to avoid unnecessary in-person reassessments.

Those who met DSM IV criteria for MDD and all the remaining inclusion/exclusion criteria during the in-person diagnostic assessment were invited to participate in the treatment phase. Those who provided written informed consent subsequently completed a baseline examination covering demographic, medical, psychiatric, functional, and environmental variables (Table 1).

The consultants encouraged us to generate “friendly competition” among the sites in order to maximize screening and enrollment. For example, during monthly committee meetings we reported on the number screened and enrolled at each site. The secure tracking website included a graphic that depicted the extent to which each site contributed to overall study accrual. We also explored ways to incentivize critical study activities. While it is unethical to provide financial rewards for increased recruitment in human subjects research, it is ethical to pay sites more if they performed more work during the past year. Metrics were thus created to evaluate site performance. Therefore the steering committee agreed to withhold 10% of the total funds each year in years 2–5 and to disburse these funds in proportion to the amount of work each site performed during the previous year. The amount of work performed each year was based on the number of screenings conducted and subjects enrolled that year. The total work performed at each site each year equaled: the standard time it takes to perform each screening times the number of people screened that year, plus the standard time it takes to treat each enrolled person times the number of people enrolled that year.

Within 1.5 years we recognized that our overall recruitment rate was falling below the benchmark of four subjects per month needed to reach our target sample within 5 years. Therefore, we used monies

carried over from start-up funds and the first budget year to add a fifth site, BIR. Including BIR was sufficient to boost our recruitment into the target range temporarily. However, by the second half of year four the original sites began exhausting their pool of unscreened persons. We did not rescreen nondepressed individuals unless their PHQ-9 score was in the borderline range of 8–9 because we thought the yield would be very low. Thus, we added another site, the University of Miami, to reach the enrollment goal.

Phase 2: treatment design and implementation

Randomization and treatment design considerations

Study participants were randomly assigned to active treatment (venlafaxine XR) or inactive placebo control on a 1:1 basis. Treatment assignment was block randomized and stratified by site. Because response to treatment may differ between persons with versus without a prior history of major depression or a prior history of substance dependence,⁷¹ randomization was also stratified by these factors. The statistician generated randomization logs for each site and sent them to each hospital pharmacy via the IDS. After subjects completed the baseline assessment, prescribers contacted the study pharmacist at their site, who wrote the patient’s name on the next available line of the randomization log for the appropriate stratum and sent the starting dose of the assigned study drug to the prescriber.

Certain design elements merit explanation. Our trial was 12 weeks rather than 8 or 10 weeks in duration based on observations that people with neurological conditions may take longer to respond to antidepressant therapy.³² Given the potential for non-specific effects of treatment to inflate the placebo response rate, we standardized interactions between subjects and study staff in ways designed to enhance retention but minimize spontaneous improvement. We planned to have five interim visits as a compromise between safety concerns (where more frequent is better) and the desire to minimize improvement that tends to occur in response to repeated measurement, generic interactions with clinical staff, and the tendency of subjects to (unconsciously) conform to expectations of improvement (for which less frequent contact is better). Based on consultant input, study staff was instructed to interact with subjects in a polite, but professional and business-like manner. Staff were asked not to be interpersonally therapeutic. We allowed some interim visits to be conducted via telephone and sent prescriptions to subjects by overnight mail, because in this population transportation to the study site was expected to be a barrier to participation.

Adherence to treatment and trial monitoring

We monitored response to treatment on the tracking website. Early in the trial we observed a 100% response rate at one site. An investigation determined that this site had a higher than average rate of in-person interim visits and inadvertently provided subjects (who were often isolated in rural areas) with extra non-specific clinical support. Subsequently we reemphasized the importance of maintaining a more business-like relationship with subjects. We proscribed the provision of any additional help to study participants and standardized the frequency of in-person (weeks 3, 6, 10, and 12) versus telephone (weeks 1 and 8) assessments across sites.

At baseline, the pharmacist dispensed the assigned medication and delivered it to the study prescriber, who placed daily dosages into a weekly pillbox provided by the study. Subjects were instructed to take the medication with food in the morning to minimize gastrointestinal side effects or insomnia. Regular follow-up visits served to monitor depression symptoms and side effects as well as to promote medication and protocol adherence. We used pill counts to monitor adherence to the study drug. Participants were asked to bring unused medication to all in-person interim visits.

Titration schedule

The initial study medication titration plan followed the principle of “start low, go slow” as a means of maximizing the tolerability of and adherence to the study medication. The starting dose (37.5 mg/day) was half of the typical starting dose. The dose was increased to 75 mg/day during weeks 1–3 and to 150 mg by week 6. The consultants countered that this slower titration schedule meant that subjects would be exposed to the target dose (150 mg/day or higher) for only 6 weeks, and that this might limit drug titration and reduce the potential efficacy of venlafaxine XR. Therefore, a flexible dosing plan was designed that also started low, but allowed more rapid dose increases if side effects were minimal or easily tolerated. In the new plan the dose was increased to 75 mg/day at week 1, to 150 mg/day at week 3, and to 225 mg/day at week 6, if tolerated. The dose could be increased up to 300 mg/day during weeks 8–10 if the response to treatment was not adequate (i.e. the PHQ-9 score was still greater than 50% of baseline). The plan permitted temporary downward adjustment of the dose to reduce side effects.

Tolerability of the study medication was assessed at each follow-up using a standard list of previously reported general side effects of venlafaxine XR as well as SCI-specific side effects that were anticipated (e.g. spasticity). Subjects were asked what side effects they

noticed followed by questions regarding whether they experienced specific side effects. Dates and severity of side effects were recorded. We found that educating patients that side effects are often transient as well as temporarily adjusting medication doses to help mitigate side effects were important strategies to maximize participant adherence and retention.

Unblinding procedures and continuity of care issues

All participants and study staff, with the exception of the pharmacists who dispensed study drug based on the randomization log, were kept unaware of participant treatment condition. The consultants recommended that we not unblind any subjects until the last subject completed the study because this is the best way to prevent study staff from learning to detect the condition to which participants were assigned. However, the investigators thought that it was clinically and ethically important to unblind subjects after 12 weeks in order to provide them with clear guidance about future depression treatment. To mitigate the risk of unblinding study personnel, all sites identified prescribing clinicians who were not affiliated with the study to unblind subjects after the 12-week assessment. At the 8- and 10-week assessments, study staff worked with subjects to identify primary care providers or other prescribers to whom they could be referred for continuing care after the trial, if needed. After the final outcome assessment the unblinder opened a sealed envelope sent from the study pharmacy that indicated the person's study condition. The unblinder followed an algorithm based on what condition the person was in and whether they responded to that treatment (i.e. experienced at least a 50% decrease in symptom severity). Placebo responders were told that they recovered without active medication and should continue to watch for recurring symptoms. Placebo non-responders were offered 12 weeks of free treatment with venlafaxine XR at the study site or immediate referral to their primary physician or another community resource for further treatment. Venlafaxine XR non-responders were given a slow tapering prescription and referred back to their primary physician or community resource with guidance on pursuing alternative treatments. Venlafaxine XR responders were given an additional 2-week prescription of venlafaxine XR and referred back to their primary physician for maintenance therapy.

Data analyses

Power analysis

The original power analysis was based on a systematic review of antidepressant treatment in people with

physical illness.⁹¹ We predicted that the response rate (percent who achieve at least a 50% decrease in depression severity on the HAM-D from baseline to 12 weeks) would be 60% in the active treatment group and 35% among placebo controls. Fixing the power of the study at 80% and the type I error rate (two-tailed) at 0.05, we needed 140 participants (70 subjects per group). We planned to recruit a larger sample ($n = 84$ per group) to account for drop-outs (expected to be about 15%) and to permit subgroup analyses. The consultants thought that a 25% difference in response rate between treatment and controls was optimistic and that the study could be underpowered. They recommended that we increase the power by using the HAM-D as a continuous measure and include data from all interim visits in the outcome analysis. They also noted that we should account for the two intended interim efficacy analyses, which we did using O'Brien-Fleming group sequential boundaries.⁹² This resulted in a significance level at the final analysis of 0.046 with the sample size increasing to 72 completers per group to maintain the same power. With the actual sample size of 126 completers, the study would have 80% power to detect the specified between groups difference in response rate. With the change to the mixed model regression for the primary analysis (see below), we expected the power would be somewhat higher for a corresponding treatment effect.

Data analysis plan

The original primary analysis was a logistic regression comparing response rates in the two groups while controlling for site, prior history of major depression, and lifetime history of substance dependence as well as any baseline characteristics that were found to differ between groups in a preliminary analysis. The consultants recommended that we use a mixed model regression that treats the outcome measure as a continuous variable and includes outcome data from all of the interim assessment time points rather than a logistic regression that predicts only the final (12-week) endpoint category, responder versus non-responder.

Database management

We constructed a secure on-line tracking database to summarize screening and treatment phase accrual, key inclusion and exclusion data, and treatment phase data that were needed to monitor study progress. A separate statistical database was built for data analysis. Data from the tracking database could be uploaded into the statistical database. The remainder of the study data was entered into a version of the statistical database at each site. These updated data files would

then be sent back to the lead center via a secure drop-box and merged into a unified dataset by the data manager. Quality control checks were completed regularly to ensure proper data input and accuracy.

Blinded trials results

Subject recruitment and retention

The six sites completed a total of 2536 screens, randomized 133 participants and retained 126 (95%) at the 12-week primary outcome assessment (see Fig. 2). The study is now complete and primary data analysis is underway. The ratio of persons screened to enrolled was much higher than we anticipated; almost 20 persons had to be screened to enroll one trial participant. Major reasons that potential subjects were excluded were: PHQ-9 scores less than 10 ($n = 1638$), residing more than 100 miles from the site ($n = 57$) and currently receiving evidence-based treatment for depression ($n = 56$). We enrolled 79% of the target sample size. Because the retention rate was much better than anticipated (95% versus 85%), the number of people who completed the trial and provided 12-week outcome data was 90% (126 of 140) of our goal.

Sample characteristics

Characteristics of the final sample are presented in Table 2. Mean age was 40 years, 74% were men, 57% were non-Hispanic white, 32% were non-Hispanic black and 8% were of Hispanic ethnicity. About 53% of the sample had paraplegia, 53% had complete injuries and participants were an average 11 years post-injury. Compared to demographic characteristics of the SCIMS as a whole,⁹³ this sample is somewhat more likely to be black, less likely to be white, more likely to have cervical and complete injuries, and more likely to have been injured through violence.

Nearly all subjects (99%) had current MDD while 1 (1%) had current dysthymia without MDD (see Table 3). Fifty-six percent of the sample reported a prior history of MDD, 48% reported probable posttraumatic stress disorder (PTSD), 58% reported generalized anxiety, 44% had a lifetime history of substance dependence, and 21% reported current alcohol abuse. We excluded persons with current drug dependence, but other drug use was common. Current drug use in the sample included marijuana (32%), sedative/hypnotics (37%), and opioids (48%). Ninety-three percent of the sample reported chronic pain and 53% reported three or more pains. Average pain intensity at the worst pain site was in the severe range (7.1 out of 10) while pain interference was in the mild-to-moderate range.⁹⁴ Mean satisfaction with life (12.3 ± 5.3) was well below the mean for the SCIMS sample at 10 years after

Figure 2 Study flow.

injury (20.9).⁹⁵ Domains of community participation as measured by the Craig handicap assessment and reporting technique (CHART) were all modestly lower than in the overall SCIMS sample, with the exception of economic self-sufficiency, which was much lower in this sample (50.8 ± 37.2) versus the SCIMS sample at 10 years after SCI (61.8). Total self-reported environmental barriers on the Craig Hospital inventory of environmental factors (CHIEF) Short form (1.8 ± 1.4) were greater than the mean from normative data on this measure.⁹⁶

Seven people (5%) dropped out of the study and did not complete the 12-week outcome assessment. Reasons for dropping out were: allergies to the study medication; severe gastrointestinal problems; not wanting to “wait” and see if he was on a placebo; extreme sleepiness; a serious decline in health, not thought to be study related; and an episode of self-harm and subsequent psychiatric treatment. One person dropped out for unknown reasons. He attended only the baseline assessment and did not return or respond to attempts to contact.

Discussion of lessons learned

Ability to detect changes

We designed and carried out a multi-site trial in order to determine the efficacy and tolerability of venlafaxine

XR for MDD after SCI. Secondly we wanted to determine whether venlafaxine improved pain and several other outcomes in people with SCI and MDD. The trial’s ability to determine efficacy hinged on a number of key factors, some of which were quite challenging. Recruitment was indeed challenging. The six sites had to screen about 20 people to enroll each of the 133 randomized participants. On the other hand, excellent subject retention (95%) resulted in a final sample of completers that was 90% of our goal. As a result, we will have 80% power to detect between groups differences based on our original analysis plan and greater power based on the mixed model regression that will constitute the primary analysis. We also expect to have reasonable power to detect whether *a priori* subgroups respond differentially to treatment, e.g. those with a history of substance dependence and those with no prior history of MDD. Since the prevalence and severity of comorbid pain are high, we may have a reasonable chance of detecting a drug-related improvement in pain. Another factor to consider is measurement sensitivity. Based on what is currently available we believe we chose the best outcome measures to study depression in persons with SCI. Spontaneous improvement can become a major barrier to detecting between-groups differences in depression treatment

Table 2 Demographic and injury characteristics (N = 133)

Variable	Overall N = 133
Site	
1 – University of Washington, Seattle, WA	14 (11%)
2 – University of Alabama, Birmingham, AL	28 (21%)
3 – University of Michigan, Ann Arbor, MI	20 (15%)
4 – Rehabilitation Institute of Chicago, Chicago, IL	45 (34%)
5 – Baylor Institute for Rehabilitation, Dallas, TX	21 (16%)
7 – University of Miami, Miami, FL	5 (4%)
Age (years)	
Mean (SD), range	40 (11), 18–63
18–29	30 (23%)
30–44	54 (41%)
45–59	47 (35%)
≥60	2 (2%)
Sex	
Female	34 (26%)
Male	99 (74%)
Race	
Non-Hispanic White	76 (57%)
Hispanic or Latino	10 (8%)
Non-Hispanic Black	42 (32%)
Asian/Pacific Islander	1 (1%)
Other	4 (3%)
Education	
Did not complete high school	21 (17%)
Completed high school	106 (83%)
Unknown	6
Marital status	
Never married	70 (53%)
Married	41 (31%)
Divorced/separated/widowed	21 (16%)
Unknown	1
Employed	
No	109 (83%)
Yes	22 (17%)
Unknown	2
Cause of injury	
Fall	20 (15%)
Vehicular	48 (36%)
Violence	42 (32%)
Other	22 (17%)
Unknown	1
SCI level of injury	
Cervical	62 (47%)
Thoracic	58 (44%)
Lumbar	12 (9%)
Sacral	0 (0%)
Unknown	1
ASIA Impairment Scale	
A – Complete injury	71 (53%)
B – Incomplete	20 (15%)
C – Incomplete	12 (9%)
D – Incomplete	30 (23%)
Time since injury	
Mean (SD) years, range	11 (11), 0–43
≤12 months post-SCI	10 (8%)
>12 months post-SCI	123 (92%)

trials. To address this issue, we required subjects to report significant depressive symptoms on two occasions at least 10 days apart and to meet DSM IV criteria for MDD or dysthymia. We also asked subjects to guess if they were

assigned to the placebo or treatment group to determine whether awareness of their treatment condition could have influenced study outcomes.

This study illustrates both opportunities and challenges associated with conducting rigorous, adequately powered trials in this area. In terms of opportunities, this study shows that the NIDRR-funded SCIMS program can serve as a platform from which to launch multi-site clinical trials that are not industry funded. Further, the study confirms the potential of the NIDRR SCIMS collaborative research program to conduct definitive efficacy trials, as well as the ability to collaborate effectively in order to achieve high inter-site reliability in the use of outcome measures that involve clinical judgment, high rates of data completeness, excellent subject retention, and good data and subject safety monitoring. The sites demonstrated access to and the capacity to screen an extraordinary number of people with SCI. The study suggests that human subjects review boards may approve controlled trials of therapies that are already accepted as part of standard care, but lack evidence for efficacy in people with SCI. The way the study was conducted, with several waves of survey research modules attached to the study screening arm, is one way to add value to expensive treatment trials.

The study also illustrates important challenges facing multi-site investigations. We underestimated the number of people we would need to screen in order to recruit a sufficient sample size. Were it not for the exceptional efforts of the study staff, generous funding from NIDRR, permission to add other non-SCIMS sites to the study group, and approval to carry forward unobligated funds into a no-cost extension year, recruitment into the study would have been inadequate.

The formative review consultants provided critical guidance in conducting multi-site studies and in evaluating the efficacy of psychiatric medications. Their input led to significant changes in study procedures and how the trial was conducted, changes that may make a difference in the ultimate outcome of the study. Given the relatively small numbers of people with SCI at any one site, multi-site collaborations will likely be required for many definitive trials in the future. Until conducting multi-site trials becomes more commonplace within SCI rehabilitation, it may be useful to employ outside experts for multi-site studies. Teams who have conducted multi-site trials should be encouraged to write and speak about lessons learned. Other ways of disseminating information about conducting multi-site studies should be considered.

Traditional RCTs like we conducted have their drawbacks. Half of participants in a non-cross-over trial do

Table 3 Baseline clinical characteristics (n = 133)

Variable	N (%) or mean (SD)
Psychiatric disorders (SCID)	
Current major depressive disorder	132 (99%)
Current dysthymia	1 (1%)
Depression severity – mean (SD)	
HAM-D	19.7 (5.4)
SCL-20	1.97 (0.65)
PHQ-9	16.5 (4.4)
Depression history	
No prior history of depression	59 (44%)
Pre-injury history of depression	41 (31%)
Post-injury history of depression only	33 (25%)
Number of prior major depressive episodes	
Median (inter-quartile range)	1 (0, 1)
0	59 (44%)
1	42 (32%)
2	26 (20%)
3+	6 (5%)
Unknown	3
Depression-related disability	
Sheehan Disability Scale – mean (SD)	19.7 (9.0)
Work/school	6.9 (3.4)
Social life	6.4 (3.4)
Family life/home responsibilities	6.4 (3.3)
PTSD symptoms	
PCL-C total – mean (SD)	44.6 (13.0)
Probable PTSD (≥ 45)	62 (48%)
Current anxiety	
PHQ panic screen positive – n (%)	7 (5%)
GAD-7 total – mean (SD)	11.2 (5.3)
GAD-7 screen positive (≥ 10) – n (%)	76 (58%)
Current alcohol abuse	
AUDIT-C positive men (≥ 4) – n (%)	22 (22%)
AUDIT-C positive women (≥ 3) – n (%)	6 (17%)
Current drug use (WHO-ASSIST Q1)*	
Tobacco products	55 (47%)
Cannabis	37 (32%)
Cocaine	7 (6%)
Stimulants	1 (1%)
Inhalants	0 (0%)
Sedative/hypnotics	43 (37%)
Hallucinogens	0 (0%)
Opioids	56 (48%)
Unknown	16
Pain	
Number of pains	
0	9 (7%)
1	13 (10%)
2	39 (30%)
3 or more	70 (53%)
Unknown	2
Average intensity worst pain (0–10 NRS)	7.1 (2.1)
Average interference worst pain (0–10 NRS)	5.6 (2.7)
Community participation	
CHART-SF	72.8 (17.0)
Physical independence	73.7 (26.2)
Cognitive independence	80.6 (27.2)
Mobility	72.0 (23.6)
Occupation	50.8 (37.2)
Social integration	84.6 (23.4)
Economic self-sufficiency	75.3 (30.4)
Environmental factors	
CHIEF-SF	1.8 (1.4)
Policies	1.8 (2.4)
Physical/structural	2.5 (2.2)

*Continued***Table 3 Continued**

Variable	N (%) or mean (SD)
Work/school	0.7 (1.5)
Attitudes/support	1.5 (1.8)
Services/assistance	1.8 (1.9)
Life satisfaction	
Satisfaction with life scale	12.3 (5.3)
Health-related quality of life	
SF-12 physical health composite	35.6 (12.9)
SF-12 mental health composite	31.1 (10.5)
Social support	
MOS Social Support survey	65.3 (23.2)
Tangible	73.9 (24.5)
Affectionate	70.8 (29.5)
Positive social interaction	63.2 (29.8)
Emotional or informational	60.6 (26.4)

*The frequency of other drug use is likely an underestimate because at one site examiners recorded only one drug used. GAD-7, generalized anxiety disorder-7; SCL-20, symptom checklist-20.

not receive the active intervention, a barrier at times for some in terms of their willingness to participate. In behavioral studies, credible control conditions are more difficult to fabricate than is the case in drug studies. Accordingly, a number of alternative research designs have been proposed.

Alternatives to the RCT design are being encouraged and considered by many for practical and logistical reasons. At the most discrete level, single case, multiple baseline designs are gaining increased acceptance.⁹⁷ Expanding that concept to the institutional level, others have argued for “practical clinical trials” which utilize “multiple baseline across settings” designs where each institution receives the intervention, but the timing of implementation is staggered across institutions to control for secular trends, measurement reactivity, temporal effects, and other potential confounding factors.⁹⁸ Practice-based evidence research designs have also been utilized to identify empirically the most effective interventions across therapists and settings.⁹⁹ “Head to head” comparisons of a new treatment versus standard of care may be more acceptable to potential subjects and provide important information where a credible placebo equivalent control condition cannot be mounted. In a field like Rehabilitation where samples within a given institution are likely to be small, and behavioral interventions are the focus of interest, RCTs may not always be feasible, and therefore greater consideration will need to be given to alternative designs.

As we anticipated, the sample was characterized by a high degree of medical and psychosocial comorbidity, factors that may be associated with poor response to antidepressants. These include current alcohol abuse (21%), current PTSD symptoms (48%), unemployment

(83%), and persistent pain (94%). Future studies of treatments for depression should consider multi-modal interventions that include more aggressive efforts to ameliorate comorbidities such as substance abuse, PTSD symptoms, and chronic pain.

Conclusions

SCI clinicians currently base depression treatment decisions on generic side effect profiles and other “patient-specific variables” rather than on empirically established efficacy and risk. Results from this trial may be able to show whether venlafaxine XR is effective in people with SCI diagnosed with MDD. These findings could be used to promote more widespread and aggressive screening for and treatment of MDD and potentially reduce the overall burden of depression in this population. Furthermore, successful depression treatment may result in numerous other secondary benefits in terms of health, participation, and QOL. Alternatively, if this adequately powered trial does not show that an antidepressant is more efficacious than placebo, this would set the stage for psychosocial treatment trials or trials of combined treatments, as well as subgroup analyses to determine which groups of patients (e.g. the more severely depressed) might benefit more from drug treatment. Either way, results of this study could contribute significantly to more evidence-based treatment of depression in people with SCI.

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