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Evidence-Based Data From Animal and Human Experimental Studies on Pain Relief With Antidepressants: A Structured Review

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ABSTRACT

Objective. It has been hypothesized that serotonin reuptake inhibitor antidepressants (ADs) are only weakly antinociceptive but augment noradrenergic (NA) antinociception. Thus, ADs with combined serotonergic (SN) and NA activity, (i.e., the serotonergic/noradrenergic (SN/NA) ADs) should have greater antinociceptive activity versus the NA ADs, which in turn should have more antinociceptive activity than the SN ADs. The objective of this structured review was to test this hypothesis by reviewing relevant basic science literature on the treatment of experimental pain with the above different types of ADs.

Design, Setting, Participants, Outcome, Measures. Animal or human experimental AD pain treatment studies were located by the usual search methods. For animal studies only placebo-controlled studies were included for review. For human studies only double blind placebo-controlled studies were selected for review. The animal and human studies were then sorted according to the pain model represented, e.g., neuropathic pain model. Studies were then characterized according to the type of AD utilized, and the antinociceptive outcome of the AD trial.

Results. Twenty-two animal studies and 5 human studies fulfilled the inclusion criteria of this structured review. Within the animal nonspecific pain model there were 10 SN/NA AD trials, 9 NA AD trials and 7 SN AD trials. Of these trials 100%, 88.9%, and 14.3% respectfully demonstrated a positive AD antinociceptive effect. Overall, for all the animal models there were 25 SN/NA, 9 NA, and 8 SN trials. Of these trials 92%, 88.9%, and 25% respectfully demonstrated a positive AD antinociceptive effect. For the human pain models, only the SN/NA ADs had been utilized in 7 trials. Here in 42.8% of the trials there was a reported antinociceptive effect.

Conclusions. Overall, the results of this structured review support the above hypothesis.

Key Words: Structured Review; Antidepressants; Antinociception; Chronic Pain; Serotonergic; Serotonergic/Noradrenergic; Antinociceptive Effect; Animal Pain Models

The efficacy of antidepressants (ADs) for the treatment of human chronic pain has been explored in a large number of studies. Numerous authors [1–14] have reviewed these studies in an effort to determine whether these drugs have an antinociceptive (analgesic) effect; but the results have been inconsistent. Recently, however meta-analytic evidence has indicated that ADs do indeed have an antinociceptive effect [9,10,11,15] for chronic human pain. This meta-analytic evidence has also been reviewed recently [16]. The evidence consistently indicated that ADs may have an antinociceptive effect on chronic human pain and that these drugs are effective for neuropathic chronic pain [16].

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ADs can be broken down into 3 major groups according to the degree of reuptake blockade of the 2 major neurotransmitter systems: the serotonergic (SN) and the noradrenergic (NA). Thus, most ADs are currently classified as being SN reuptake blockers, NA reuptake blockers, or both SN and NA reuptake blockers (SN/NA). NA reuptake blockers may have an antinociceptive effect [17–20], while the selective serotonin reuptake blockers (serotonergic ADs) may be ineffective [21–22]. Because of the above data, and because serotonin has a known antinociceptive effect at the level of midbrain and spinal cord [23], Max has postulated that serotonin reuptake inhibitors in themselves are only weakly antinociceptive, but augment NA antinociception [24]. ADs with combined NA and SN effects (the SN/NA ADs) may, therefore, be superior to those blocking the reuptake of only one neurotransmitter [24]. In support of this hypothesis, a recent structured review comparing SN ADs to NA and SN/NA ADs for reported antinociception in human chronic pain found that the SN/NA ADs demonstrated a more consistent antinociceptive effect across the reviewed studies [16].

If the SN/NA and the NA ADs have a stronger antinociceptive effect than do the SN ADs, there should be consistent basic science evidence (animal studies and human experimental studies) that this is indeed the case. The purpose of this structured review was to systematically review the basic science research dealing with AD antinociception to determine if this literature supports the concept that the NA and SN/NA ADs have a more consistent antinociceptive effect than the SN ADs. To the authors' knowledge this is the first such literature review.

Methods

Relevant references were located in Medline, Science Citation Index, Psych Info, and the National Library of Medicine PDQ (Physician Data Query) databases, using the MESH (Medical Subject Heading) terms *ADs* and *pain.* Each selected MESH term was exploded for all subheadings, and all retrieved references were reviewed. The searches included all languages and were conducted back to 1966, with the exception of Science Citation Index, which was searched from 1974. The upper limit of each search was 1998. A manual search of key pain journals, pain meeting abstracts, and textbooks was also performed. The following journals were reviewed in the years indicated: Pain 1975–1999; Spine 1976–1999; Journal of Pain and Symptom Management 1986–1997; The Pain Clinic 1986–1999; and Clinical Journal of Pain 1985–1999. Abstract books of the following meetings were reviewed: International Association for the Study of Pain 1981, 1984, 1987, 1990, 1993, 1996, and 1999; and American Pain Society Meetings 1982–1997. Three pain textbooks were reviewed for possible references: Evaluation and Treatment for Chronic Pain, G. Aronoff (Ed), 3rd Edition, 1999; Handbook of Pain Management, C.D. Tollison, J.R. Satterthwaite, J.W. Tollison (Eds), 2nd Edition, 1994; and Textbook of Pain, P. Wall, R. Melzak (Eds), 3rd Edition, 1993.

Any identified experimental ADs pain treatment studies involving humans or animals were reviewed in detail and their reference lists searched. These studies were then sorted into 2 major groups: animal and human studies. Animal studies were further sorted by the type of pain model/assay they represented: non-specific pain models, neuropathic pain model, noxious colorectal distention model, acute inflammatory model, arthritic model, and autonomy (self-mutilation model). Human experimental pain studies were sorted by the following models: heat/pressure, electric shock, sensory decision theory tasks, esophageal pain perception model, rectal distention model, and cutaneous stimulation model. Within each model, animal studies were selected for detailed review if the studies were placebo controlled or the animals served as their own controls with an inherent placebo (e.g. no drug). For human studies, only double blind placebo-controlled studies were selected for inclusion.

Selected studies were placed into table format according to the models used.

Results

Twenty-two AD pain treatment animal studies [25–46] were located that fulfilled the inclusion/exclusion criteria of this review. Five human AD pain treatment studies [47–51] that met the inclusion/exclusion criteria of this review were also located. Animal studies (Table 1) were classified according to whether the AD was reported effective or not effective for pain. The AD used in each study was classified as SN, NA, or SN/NA AD. The same scheme was used for human AD experimental pain studies (Table 2).

For the nonspecific pain model in Table I, there were 10 SN/NA AD trials [25–29,40,45] (some studies tested more than one AD). Of these 10 trials, all (100%) demonstrated an antinociceptive effect. For this model there were also 9 NA AD trials [26,28,29,39,40,42,44] (some studies tested more than one AD). Of these 9 trials, 8 (88.9%) reported

Table 1 Rat or mice pain models/assays and antidepressants shown to have or not to have an analgesic effect in these models/assays, along with references

Non-specific pain models					
• Inescapable foot shock • Paw pressure • Tail flick test • Intradermal hypertonic saline • Mouse writhing assay • Hot plate • Formalin test • Behavior pain test • Jump test	• Neuropathic pain model	• Noxious colorectal distention model	• Acute inflammatory model	• Arthritic pain model	• Autotonomy (self mutilation model)
AMI (SN-NA) EFF[25–28] IM (SN-NA) EFF[25,27,29] DE (NA) EFF[28,39,40–44] CL (SN-NA) EFF[45,40,26,26*] MA (NA) EFF[40] FL (SN) NOT EFF[46,42,43,28] NO (NA) EFF[42][29] NO (NA) NOT EFF[26] TR (SN) NOT EFF[26] PR (NA) EFF[42] CI (SN) NOT EFF[42] CI (SN) EFF[29]	AMI (SN-NA) EFF[30,31] DE (SN-NA) EFF[30,32] CL (SN-NA) EFF[30] FL (SN) EFF[32]	IM (SN-NA) EFF[33] DE (SN-NA) EFF[33] CL (SN-NA) EFF[33]	CL (SN-NA) EFF[34]	AMI (SN-NA) EFF[35] IM (SN-NA) EFF[35] AMI (SN-NA) NOT EFF[36] IM (SN-NA) NOT EFF[36]	AMI (SN-NA) EFF[37,38]

KEY: EFF = Effective for Analgesia; NOT EFF = Not effective for Analgesia; AMI = Amitriptyline; IM = Imipramine; DE = Desipramine; * = Also ↑ morphine antinociception; SN = Serotonergic; NA = Noradrenergic; S-NA = Serotonergic/noradrenergic; CL = Clomipramine; MA = Maprotiline; FL = Fluoxetine; NO = Nortriptyline; TR = Trazadone; PR = Protriptyline; CI = Citalopram.

an antinociceptive effect. For this model there were also 7 SN AD trials [26,28,29,42,43,46] (some studies [26,28,29,43,46] tested more than one AD). Of these, only one (14.3%) reported an antinociceptive effect.

For the neuropathic pain model (Table 1) there were 5 SN/NA AD trials [30–32] (some studies tested more than one AD). Of these, 5 (100%) reported an antinociceptive effect. For this model there was also one SN AD trial [32] that reported a positive antinociceptive effect.

For the noxious colorectal distention model (Table 1) there were only SN/NA AD trials. All three trials [33] (study tested more than one AD) demonstrated an antinociceptive effect.

For the acute inflammatory model (Table 1) there was only one trial [24]. Here a SN/NA AD was utilized. This trial reported an antinociceptive effect.

For the arthritic pain model there were only SN/NA AD trials. Here there were 4 trials [35,36] (some studies tested more than one AD). Two trials (50%) reported a positive antinociceptive effect.

For the autonomy model (Table 1) there were only SN/NA AD trials. Here there were 2 trials [37,38)]; all trials (100%) reported an antinociceptive effect.

Table 2 Human experimental pain models and antidepressants shown to have or not to have an analgesic effect in those models along with references (all placebo controlled)

Pain models	Antidepressants shown to have or not to have an analgesic effect
Heat and pressure	IM (S-NA) EFF: [47] (volunteers) (randomized, double blind crossover, single oral dose)
Electrical shock	IM (S-NA) EFF: [48] (volunteers) (double blind, repeated measures, single oral dose)
Sensory decision theory tasks	DO (S-NA) NOT EFF: [49] (chronic pain patients) (double blind, 4 week trial)
Oesophageal perception	IM (S-NA) EFF: [50] (volunteers) (double blind, crossover, 12 day trial) AMI (S-NA) NOT EFF [51] (volunteers) (double blind, 21 day trial)
Rectal distention	AMI (S-NA) NOT EFF: [51] (volunteers) (double blind, 21 day trial)
Cutaneous stimulation	AMI (S-NA) NOT EFF: [51] (volunteers) (double blind, 21 day trial)

KEY: AMI = Amitriptyline; IM = Imipramine; DO = Doxepin; EFF = Effective; NOT EFF = Not effective; SN-NA = Serotonergic/noradrenergic.

For all animal models taken together there were 25 SN/NA AD trials. Of these, 23 (92.0%) reported an antinociceptive effect. There were also 9 NA AD trials; eight (88.9%) reported an antinociceptive effect. Finally, there were also 8 SN AD trials. Of these, only 2 (25%) reported an antinociceptive effect.

For each of the human pain models (Table 2), except the esophageal pain perception model, there was only one AD trial [47,48,49,51] (some studies reported on more than one model). The esophageal pain perception model had 2 trials [50,51]. For all the above trials only the SN/NA AD were utilized. Thus, for the whole group of human pain models there were 7 trials [47–51] (some studies reported on more than one AD). Of these, only 3 (42.8%) reported an antinociceptive effect.

Discussion

The 3 types of ADs appear to have differential rates of effective antinociception, at least within one animal pain model (nonspecific). Within the animal models, all 3 AD types have *some* antinociceptive effect. The SN/NA ADs are effective for 100% of the trials in all the animal pain models, except for the arthritic model. Where enough trials were reported (the nonspecific animal models) to make a direct comparison between the 3 types of ADs, SN/NA ADs were superior (100%) to the NA (88.9%) ADs, which were superior to the SN (14.3%) ADs for antinociception. A similar observation relates to the results using all the animal models as one group. The antinociceptive effect for SN/NA ADs in human pain models, however, appears to be about 50% lower (92.0% versus 42.8%) than in animal models. These observations provide additional support for the widely held belief that ADs have an antinociceptive effect. However, this is the first time this line of evidence has been reviewed. In addition, these observations support the hypothesis put forward by Max [24], and outlined in the introduction, that NA ADs are more antinociceptive than SN ADs, while SN/NA ADs are superior to both.

There is support for this hypothesis from human chronic pain treatment studies. A recent structured review [16] found that the SN/NA, NA, and SN ADs were reported to have an overall antinociceptive effect (for all types of chronic pain except neuropathic) in 77.6%, 71.4%, and 48% of trials, respectfully. Isolating human chronic pain treatment studies where head-to-head comparisons have been made between the different types of ADs for an antinociceptive effect, the authors found 5 such non-neuropathic chronic pain treatment studies [52–56]. (Non-neuropathic chronic pain treatment studies were isolated because Max [24] developed his hypothesis based on neuropathic pain AD treatment results.) Langemark et al. [52] compared clomipramine (SN/NA) to mianserin (SN) for the treatment of tension headache in a variable dose procedure. Loldrup et al. [53] compared clomipramine (SN/NA) to mianserin (SN) for the treatment of tension and cluster headache in a standard dose protocol. Frank et al. [54] compared amitriptyline (SN/NA) to desipramine (NA) to trazadone (SN) for the treatment of rheumatoid arthritis in a standard dosage protocol. Rani et al. [55] compared fluoxetine (SN) to amitriptyline (SN/NA) for the treatment of rheumatoid arthritis in a standard dosage protocol. Atkinson et al. [56] compared maprotiline (NA) to paroxetine (SN) for the treatment of chronic low back pain in a variable dose protocol.

Review of these 5 studies indicated that 3 of them [52,54,56] supported the hypothesis, two [52,54] by demonstrating that the SN/NA ADs had an antinociceptive effect versus no effect for the SN ADs. In the third study [56], the NA AD (maprotiline) had an antinociceptive effect versus no effect (equal to placebo) for the SN AD paroxetine. This last study [56] was extremely well controlled for methodological problems known to have limited the generalizability of previous AD antinociceptive studies for human chronic pain. The remaining two studies [53,55] did not support the above hypothesis, indicating that the SN and the SN/NA ADs had an equal antinociceptive effect.

As demonstrated in this review, it is more difficult to demonstrate AD antinociceptive efficacy in human than in animal studies. Therefore, although these 5 human chronic pain treatment studies vary in quality, their data offer strong support (in addition to the data presented in this structured review from animal and human experimental studies) for the hypothesis that SN/NA ADs have a superior antinociceptive effect.

If SN ADs indeed have less antinociceptive effect than NA or SN/NA ADs, what accounts for this difference? Max [24] has postulated that SN ADs are only weakly antinociceptive. However, the serotonin (5-HT) receptor is very complex, having a number of receptor subtypes [57]. At present, it is not clear which 5-HT receptors are most involved in nociceptive transmission [57]. For 5-HT antinociceptive activity, the 5-HT_4, 5-HT_3, and 5-HT_2 receptor subtypes could be involved [57,58]. Most SN AD, such as paroxetine, block 5-HT, 5-HT_2 and 5-HT_3 reuptake, but do not necessarily block reuptake at the other receptor subtypes. This could, in

part, explain the alleged weak antinociceptive effect of the SN ADs: perhaps SN AD efficacy depends on whether that AD does or does not have affinity for 5-HT receptors responsible for antinociception.

Some limitations in structured reviews have been identified that could have detracted from the validity of this review. First, not all published studies are easily retrieved. Research has indicated that a large percentage of relevant studies can be missed if electronic retrievals such as Medline searches [59,60] are used. Adjunct search methods, such as hand searching of key journals and reviews of bibliographies, should also be used [59,60]. Because we used these processes, we are relatively certain that we found most of the relevant studies. However, we cannot claim that all relevant studies were located. The second feature of our review that may have affected its validity was study selection. Studies were selected for inclusion based on only one criterion: they were placebo controlled. Quality factors were not taken into account. A third problem with this review was the use of a vote counting procedure, which does not take into account the number of patients or animals in the study, and thus, its statistical power. This is a general problem with all reviews that are not meta-analyses. Finally, some of the non-specific animal model tests may have been misinterpreted. This problem relates to the tail-flick test, which can be misinterpreted in other temperature tests [57]. At present, it is impossible to identify the studies affected.

Future studies wishing to test Max's hypothesis [24] should proceed in two ways. More direct head-to-head comparisons between SN/NA ADs, NA ADs, and SN ADs should be performed in well-defined animal pain models and in human experimental models. Similar studies should be performed in well-defined human chronic pain groups. The second approach should utilize and compare SN ADs with differing 5-HT receptor affinities for the antinociceptive effect.

Conclusions

The results of this review support Max's hypothesis on differing antinociceptive properties of the different AD groups; however, this issue requires further study.

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