The Relationship Between Type of Antidepressant and Neurovegetative Symptoms in Adult Unipolar Nonpsychotic Depression: An Opinion Survey

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Abstract

The bi-directional nature of the neurovegetative symptoms of depression, as well as the differential response to antidepressant medications, underscore the existence of possible subtypes of this disorder. This study surveyed 56 physicians practicing psychiatry in Hawaii for opinions regarding the most effective antidepressant medication for the following symptoms: hypersomnia vs. insomnia, psychomotor agitation vs. retardation, and gain vs. loss of appetite or weight. Fluoxetine was found to be the drug of choice for weight and appetite gain, hypersomnia, and psychomotor retardation. Mirtazapine was viewed as most effective for weight and appetite loss. Trazodone was found most effective for insomnia and nefazodone for psychomotor agitation. It is concluded that subtyping of depression should be investigated at the symptom level and the generalizability of the effects of each specific compound should be tested.

The heterogeneous nature of depression has led to research designed to identify subtypes based on diagnostic criteria, physiological and biochemical markers, etiological evidence, and differences in response to treatment.[1,2,3,4] Identifying differential responses to antidepressant medications has become an important approach to subtyping given the rapid increase in prescribing these drugs in recent years.[5] While there have been surveys attempting to identify factors affecting physician choice of specific antidepressants, such as severity of depression and comorbidity with anxiety,[6] little is known about the relation of choice and presence of particular depressive symptoms.[3,4] The purpose of the present study is to explore subtypes in terms of prescribing habits for a subset of symptoms that differ markedly across cases of depression, the neurovegetative symptoms that can occur in a bi-directional manner (hypersomnia vs. insomnia, psychomotor agitation vs. retardation, and gain vs. loss of appetite or weight).

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It is widely accepted that the major antidepressant groups differentially alter several serotonergic and noradrenergic neurotransmitter systems, directly and indirectly.[7] These antidepressants include monoamine oxidase inhibitors (MA0Is), tricyclic antidepressants (TCAs), and second generation compounds (SGCs; including selective serotonin reuptake inhibitors [SSRIs]). Given the potential differential effects of antidepressants, it follows that some medications would be relatively more effective with certain symptoms of depression,[3,4] particularly the bi-directional ones involving either an increase or decrease in neurovegetative behaviors.

In a recent review, Mongeau et at.[7] concluded agents that are 5-HT or noradrenaline reuptake inhibitors are equally effective for treatment of depression, but this conclusion was based on research that did not measure drug effects upon particular depression symptoms. Research on the effects of different antidepressants upon atypical depression, whose definition includes the reversal of the usual pattern of bi-directional symptoms mentioned above, has been mixed,[8,9] although one laboratory [10] has found the MAOI phenelzine to be superior to the TCA imipramine.

Only a few studies have explored the effects of the newer generation of antidepressants upon bi-directional symptoms.[11] Equivocal findings may be due to the following methodological limitations of these studies: (1) use of global improvement scores to evaluate treatment outcome, rather than measures of the effect of antidepressants upon each bi-directional symptom; (2) inclusion of only one drug within the type(s) under investigation, limiting generalizability to other compounds classified within the same type of antidepressant; (3) definitions of atypical depression that include not only neurovegetative behavior, but also premorbid personality characteristics such as rejection sensitivity [8]; and (4) use of heterogeneous and global criteria to label atypical depression that can include any two of four symptoms, which obscures information on the precise bi-directional symptoms involved. For example, using the Columbia criteria [10] a case of depression could be labeled atypical if weight gain and psychomotor retardation (severe fatigue, leaden paralysis) are present. It would be unknown in this case if sleep was increased, decreased, or unchanged.

Because little is known about specific antidepressant drug-symptom relations, the purpose of this study was to survey psychiatrists

about their prescription habits and clinical opinion of the most effective drug for bi-directional symptoms of unipolar nonpsychotic depression among adults. If physicians report symptom-specific efficacy of particular antidepressants, these observations would justify animal model testing and the conduct of clinical trials designed to create specific drug-symptom profiles along the lines proposed by Stahl.[4]

Method

Subjects. Participants were 56 psychiatrists practicing in Hawaii. Their medical specialties were as follows: 37 (62%) general psychiatry, 2 (3%) child psychiatry, 1 (2%) rehabilitative medicine, and 16 (27%) multiple psychiatric specialties. The mean age was 51.20 years (SD = 10.79) and 45 (80%) were male and 12 (20%) female. The mean years since licensure was 21.23 (SD = 11.14). Ethnicity was 2 (3%) Pacific Islander, 1 (2%) Hawaiian-part Hawaiian, 39 (65%) Caucasian, 11 (18%) Asian, 1 (2%) mixed, and 3 (5%) other. Their employment settings included 20 (33%) private practice, 5 (8%) hospital, 1 (2%) community health center, 3 (5%) university, 3 (5%) other, and 25 (42%) multiple settings. Some participants failed to report part of the demographic information, so percentages do not add up to 100%.

Materials. A fourteen-item Opinion Survey on Use of Antidepressant Medications was developed by the present investigators. The Survey provided the respondents with the list of three MAOIs, seven TCAs, and 12 SGCs (including SSRIs) that appear in Table 1. Three items asked respondents to rate on a 5-point Likert scale the frequency of prescribing each type of antidepressant for adults presenting with unipolar nonpsychotic depression defined as major depressive disorder, dysthymia, or depressive disorder not otherwise specified. One open-ended item asked what drug is most frequently prescribed by the respondent. Eight open-ended items asked the respondent to indicate the most effective medication for the following symptoms of adult unipolar nonpsychotic depression: weight loss, appetite loss, weight gain, appetite gain, insomnia, hypersomnia, psychomotor agitation, and psychomotor retardation. Two items measured diagnostic and treatment progress procedures typically used. These could include unstructured or semi-structured interview and mental status examination, structured interview, clinical rating or behavioral checklist, self-report questionnaires, and other unspecified devices. The remaining items concerned demographic information.

Table 1. Antidepressants included on the opinion survey

TRICYCLIC COMPOUNDS
Imipramine (TOFRANIL)
Desipramine (NORPRAMIN)
Trimipramine (SURMONTIL)
Protriptyline (VIVACTIL)
Nortriptyline (PAMELOR, AVENTIL)
Amitriptyline (ELAVIL)
Doxepin (ADAPIN, SINEQUAN)

SECOND-GENERATION COMPOUNDS
Amoxapine (ASENDIN)
Maprotiline (LUDIOMIL)
Trazodone (DESYREL)
Fluoxetine (PROZAC)
Fluoxetine (LUVOX)
Bupropion (WELLBUTRIN)
Sertraline (ZOLOFT)
Paroxetine (PAXIL)
Clomipramine (ANAFRANIL)
Venlafaxine (EFFEXOR)
Mirtazapine (REMERON)
Nefazodone (SERZONE)

MAO INHIBITORS
Phenelzine (NARDIL)
Isocarboxazid (MARPLAN)
Tranylcypromine (PARNATE)

Procedure. Surveys were mailed to 196 physicians with an addressed and stamped envelop. Physicians were those known by the Hawaii Medical Psychiatric Association to practice psychiatry in Hawaii. Fifty-six (29%) returned the Survey within approximately one month. Due to the anonymity of the survey, the differences between responders and nonresponders are unknown.

Results

Because the participants' reported opinions may have been affected by the assessment devices they typically use, it is important to consider these findings. In terms of establishing a diagnosis for unipolar nonpsychotic depression, 31 (52%) reported using unstructured or semi-structured interview and mental status examination, 1 (2%) self-report measures, and 23 (38%) multiple devices. In terms of treatment progress, 30 (50%) reported using unstructured or semi-structured interview and mental status examination, 1 (2%) self-report measures, 1 (2%) other devices, and 22 (37%) multiple devices.

Participants' mean ratings on a 5-point Likert scale (1 = not at all; 5 = always) of the frequency of prescribing the three types of antidepressants were 1.55 (SD = 0.60) for MAOIs, 3.79 (SD = 0.76) for SGCs, and 2.38 (SD = 0.68) for TCAs. Therefore, MAOIs were prescribed not at all to rarely, SGCs were prescribed sometimes to usually, and TCAs were prescribed rarely to sometimes. An ANOVA indicated that the means were significantly different ($p<.001$). Fisher's post-hoc least significant difference tests indicated that each mean was significantly different from the other two means when considering the familywise error rate.

When asked what drug on Table 1 they most often prescribed, 51 (83%) respondents reported SGCs and 1 (2%) reported TCAs (imipramine). The remaining respondents indicated multiple types of drugs. Of the respondents reporting specific SGCs as most commonly prescribed, 34 (52%) indicated SSRI's (sertraline, fluoxetine, and paroxetine). The number and percent of respondents reporting they most often prescribe other SGCs are as follows: 2 (3%) nefazodone, 1 (2%) trazodone, and 1 (2%) venlafaxine.

In order to test whether there is an association between antidepressant drugs and each bi-directional symptom, Chi-square analyses of expected versus obtained frequencies were conducted both for type of drug and for specific drugs. The results for each symptom are listed below and reported in Table 2. Percentages do not total to 100 due to listwise deletion of missing data.

Table 2. Significant drug-symptom associations

Symptom	Drug Type	Specific Drugs
Weight loss	SGC	Mirtazapine (REMERON)
Weight gain	SGC	Fluoxetine (PROZAC)
Appetite loss	SGC	Mirtazapine
Appetite gain	SGC	Fluoxetine
Insomnia	SGC	Trazodone (DESYREL)
Hypersomnia	SGC	Fluoxetine
Psychomotor retardation	SGC	Fluoxetine
Psychomotor agitation	SGC	Nefazodone (SERZONE)

Note: SGC = second generation compound; trade names for drugs are in parentheses

Weight loss. For type of drug, 18 (30%) reported TCAs while 29 (48%) reported SGCs to be most effective (Chi-square = 73.62, df = 2, p < 001). Of the specific drugs indicated as most effective, most (18%) reported mirtazapine (Chi-square = 16.13, df = 4, p < .003).

Weight gain. For type of drug, 2 (3%) reported TCAs while 46 (77%) reported SGCs to be most effective (Chi-square = 63.72, df = 2, p <.001). Of the specific drugs, most (43%) reported fluoxetine as most effective (Chi-square 61.31, df = 5, p <.001).

Appetite loss. For type of drug, 17 (28%) reported TCAs while 30 (50%) reported SGCs to be most effective (Chi-square = 69.99, df = 2, p <.001). Of the specific drugs, most (17%) reported mirtazapine as most effective (Chi-square 21.67, df = 5, p <.001).

Appetite gain. For type of drug, 1 (2%) reported TCAs while 46 (77%) reported SGCs as most effective (Chi-square = 65.25, df = 2, p <.001). Of the specific drugs, most (48%) reported fluoxetine as most effective (Chi-square = 76.97, df = 4, p <.001).

Insomnia. For type of drug, 7 (12%) reported TCAs while 44 (73%) reported SGCs as most effective (Chi-square = 58.46, df = 2, p <.001). Of the specific drugs, most (33%) reported trazodone as most effective (Chi-square = 38.52, df = 5, p < .001).

Hypersomnia. For type of drug, 1 (2%) reported TCAs, 44 (73%) reported SGCs, and 4 (7%) reported MAOIs as most effective (Chi-square = 277.10, df = 3, p <.001). Of the specific drugs, most (40%) reported fluoxetine as most effective (Chi-square = 56.13, df = 5, p <.001).

Psychomotor retardation. For type of drug, 5 (8%) reported TCAs while 44 (73%) reported SGCs as most effective (Chi-square = 58.47, df = 2, p < .001). Of the specific drugs, most (38%) reported fluoxetine as most effective (Chi-square = 41.78, df = 4, p <.001).

Psychomotor agitation. For type of drug, 13 (22%) reported TCAs while 36 (60%) reported SGCs as most effective (Chi-square = 57.61, df = 2, p < .001). Of the specific drugs, most reported nefazodone (22%) as most effective (Chi-square = 26.39, df = 5, p <.001).

Discussion

The results of this survey must be viewed within the limitations of the naturalistic survey method employed. The participants were a convenience sample of physician volunteers whose names were on the mailing list of the Hawaii Psychiatric Medical Association and were not randomly selected. The differences between responders and nonresponders to the survey are unknown due to the desire to maintain anonymity. The survey was developed for this investigation and is of unknown reliability and validity. We report aggregate opinion data only, rather than objective case-by-case treatment and symptom profiles and outcome measures, so our findings are subject to reporting biases. In addition, many of the survey questions obtained frequency data on drug-symptom relations rather than Likert-like independent ratings in order to keep the survey brief (ratings would have required an additional 176 questions). Finally, we did not assess a range of patient and physician factors that could affect prescribing habits, such as other depression symptoms, side effects, insurance, marketing factors, past response to other drugs, Axis II co-morbidity[12] medical condition, type of psychiatric practice (e.g. private or institutional), type of training (e.g., biological-psychotherapy focus), and years of experience.

We found that the most common type of antidepressant medication prescribed for unipolar nonpsychotic depression and for each specific bi-directional neurovegetative symptom was a SGC (especially SSRIs). This finding is consistent with prior investigations of prescribing habits reporting that SSRIs were chosen most frequently by psychiatrists for outpatient depression regardless of patients' age, sex, race, or payment source.[5]

Our most interesting findings concerned what particular SGC was associated with specific bi-directional symptoms. Of the 12 SGCs to consider, the participants reported specific neurovegetative symptom effects for the following four compounds: mirtazapine, fluoxetine, trazodone, and nefazodone (see Table 2 for drug-symptom associations).

It is noteworthy that fluoxetine was reported as being most effective for hypersomnia, weight and appetite gain, and psychomotor retardation as these symptoms constitute a partial description of atypical depression according to the Columbia criteria.[8] Our findings are consistent with Nierenberg et. al's call for the investigation of the effects of SGCs upon atypical depression.[11] However, the Columbia criterion requires only two of these symptoms to be present, indicating the importance of investigating the effects of antidepressants at the symptom level.

The prescribing habits of the psychiatrists participating in this study indicate that clinicians tend to tailor their choices of antidepressants at least partly based upon neurovegetative symptom profiles. The reported antidepressant of choice varied as a function of the direction of change in psychomotor activity, sleep, and appetite or weight. Therefore, our findings support a subtyping or symptom-treatment profiling approach to unipolar nonpsychotic depression.[1,2,3,4]

The basis of symptom profiling by our participants of course is unknown. One possible explanation is that the clinicians are selecting compounds based upon what is known about the agent's differential effects upon certain serotonergic and noradrenergic neurotransmitter systems. For example, none of the agents in Table 2 are considered to inhibit dopamine reuptake but they do differ in terms

of sedative activity, anticholinergic activity, inhibition of norepinephrine and serotonin reuptake, and blockade of serotonergic and noradrenergic receptors.[12] Another possibility for our findings is that clinicians have also had the opportunity to observe patterns of the therapeutic and side effects of different agents upon presenting neurovegetative symptoms and prescribe accordingly. This symptom profiling would be consistent with reports of similar therapeutic and side effects in the literature. [4]

The reported differential effects of antidepressant agents as a function of presenting symptoms is inconsistent with arguments that all drugs that inhibit 5-HT reuptake are equally effective.[7] The results of this study suggest that there is a need for clinical guidelines for the choice of specific antidepressant medications based upon the particular presenting symptoms of unipolar nonpsychotic depression.[3,4] The findings support the investigation of animal models of neurovegetative symptoms of depression as well as the implementation of clinical trials that evaluate the generalizability of the effects of each drug compound across type of agent and across type of depressive symptom.

Acknowledgements

This paper was completed by the co-authors following the death of Dr. Jon Shepherd on November 23, 1998. Dr. Shepherd developed the hypotheses and general methodology for the study. We would like to dedicate this article to Dr. Shepherd who was an assistant professor in the Department of Psychology at the University of Hawaii.

We would like to thank the Hawaii Medical Psychiatric Association for providing a list of physicians practicing psychiatry in Hawaii and the participants of this study. We would also like to thank Dr. Daniel Blaine for consultation on the statistical analyses and Barbara Haia for help with inputting the data.

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