Differential Response to Chlorpromazine, Imipramine, and Placebo

A Study of Subgroups of Hospitalized Depressed Patients

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A major aim of the present study was to examine the differential effects of chlorpromazine and imipramine among various depression subgroups. Tests were made of differential drug effects among Overall et al's three empirically derived depressive subtypes, ie, anxious, hostile, and withdrawn-retarded depressives. These investigators found a tranquilizer, thioridazine, best for their anxious depressives and imipramine best for the withdrawn-retarded depressives. An examination was also made of differential drug effects among psychotic depressives, neurotic depressives, and schizophrenics with depression. As there is a tendency in this country to equate psychotic depression with endogenous depression, study findings may have some relevance for the endogenous-neurotic distinction. Proponents of this distinction have reported that imipramine is especially efficacious for endogenous depression and of little value in neurotic depressions.13,1

Finally, tests were made of differential drug effects among depressed patients categorized on the basis of sex and age (below 40 and 40 and above). Age 40 and above has been noted as one of the criteria of endogenous depression.13,14 Further, Wittenborn15 reported that female patients under 45 with paranoid features failed to respond to imipramine.

Method

Patients.—The study sample consisted of 395 female and 160 male white patients drawn from the psychiatric populations of two large metropolitan receiving hospitals (D.C. General Hospital, Washington, DC; Malcolm Bliss Mental Health Center, St. Louis), four state hospitals (John Umstead Hospital, Butner, NC; Rochester State Hospital, Rochester, Minn; Rochester State Hospital, Rochester, NY), and four private institutions (Hartford Hospital, Hartford, Conn; Mercy Douglass Hospital, Philadelphia; Philadelphia Psychiatric Center, Philadelphia; and the Sheppard and Enoch Pratt Hospital, Towson, Md). The median patient was 42 years of age and attended but did not complete high school. Eighty-five percent of the male and 89% of the female patients were or had been married. Newly hospitalized patients between 16 and 70 years of age and with no evidence of mental deficiency, chronic alcoholism, liver damage, unequivocal brain damage, cardiovascular disease, or epilepsy were admitted to the study. Project coordinators (a psychiatrist or psychologist) at each hospital also rated patients on amount of depression in verbal report, behavior, and secondary symptoms of depression. Each of these three items were rated on five-point intensity scales. For admission to the study a patient had to achieve a total score of

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at least nine, which would be the equivalent of a moderate amount of depression.

Procedure.—Drugs and Dose.—On their third or fourth day in the hospital, patients were randomly assigned to one of the three drug treatment groups. By treatment, there were 176 patients in the chlorpromazine group, 200 in the imipramine group, and 179 in the placebo group.

During the three or four day pretreatment period patients were kept off all medication. A double-blind design was in effect during the seven-week course of the study.

Doses of chlorpromazine and imipramine were raised in daily step increments to a dosage level of 600 mg of chlorpromazine and 300 mg of imipramine by the patient’s sixth day in the study. From the patient’s 7th through 30th day, the prescribing physician had the option of raising the medication to 800 mg of chlorpromazine or 400 mg of imipramine or of lowering the medication to 400 mg of chlorpromazine or 200 mg of imipramine. After the patient’s 30th day in the study, dosage was lowered in daily step increments so that patients were off medication entirely after five weeks. Final evaluations were made at seven weeks or two weeks after medication was discontinued.

Evaluations.—There were eight major evaluation instruments in the study. The Inventory of Psychiatric Complaints (IPSC), the Brief Psychiatric Rating Scale (BPRS),16 and the Inpatient Multidimensional Psychiatric Scale (IMPS)17 were completed by two psychiatrists or a psychiatrist and psychologist following an interview with the patient. The Ward Behavior Rating Scale (WBR),18 Global Ward Behavior Scales (GWBS), and an adjective checklist, the Mood Scales, were completed by a study nurse. Patients rated themselves on the Mood Scales and the Inventory of Psychiatric and Somatic Complaints. Text examiners (a study nurse or psychologist) who observed the patient during completion of the various patient self-report forms also rated the patient’s test behavior on nine items adapted from the Friedhoff Task Behavior Scale (FTBS).19

All of these instruments were rate at pretreatment and again at the end of one, two, three, five, and seven weeks of treatment. The Mood Scales and Global Ward Behavior Scales were rated at the pretreatment period and twice a week through the seventh week.

The Inventory of Psychiatric and Somatic Complaints is a modification of the Symptom Checklist20,21 with additional items sampling secondary symptoms of depression. The items on the Mood Scales were gleaned from a variety of sources.22-25 Particular emphasis was given, however, to adjectives which have reflected shifts in patient mood as a function of drug treatment22 and have differentiated depressed patients from normals.26 The Global Ward Behavior Scales was patterned after the Brief Psychiatric Rating Scales with each of the 19 items representing a major factor of psychopathology identified from prior factor analyses of the ward behavior of depressed and schizophrenic patients.26,27

Separate factor analyses were performed on the IPSC (psychiatrist), WBRS, Mood Scales (nurse), Mood Scales (patient), and IPSC (patient). A total of 52 factors were extracted from these various instruments.28 These factor scores plus the 10 IMPS factor scores, 16 BPRS items, and 19 Global Ward Behavior Scale items were the major change or criterion measures. These separate measures were rationally grouped into 12 categories of psychopathology. These included depressive mood, feelings of guilt and worthlessness, hostility, anxiety-tension, sleep disturbance, cognitive loss and subjective uncertainty, interest and involvement in activities, somatic complaints, retardation in speech and behavior, bizarre thoughts and behavior, excitement, and denial of illness.

Ratings of severity of illness and global change since the pretreatment period were also made by psychiatrists, nurses, and patients at one, two, three, five, and seven weeks.

The Three Diagnostic Groups.—Although an initial diagnosis of depression was not a prerequisite for admission to the study, the breakdown of initial diagnoses by the project coordinators was as follows: Involutional psychotic reaction (No. = 70), manic depressive reaction, depressive type (No. = 49), psychotic depressive reaction (No. = 107), schizophrenic reaction, schizoaffective type (No. = 50), schizophrenic reaction, other (No. = 32), depressive reaction (No. = 206) and other neurotic reactions (No. = 41). To test for differential effects of the three study medications among various diagnostic groups, patients diagnosed as suffering from depressive reaction or other neurotic reactions were combined to form the neurotic depressives, patients diagnosed as suffering from involutional psychotic reaction, manic depressive reaction, depressive type, and psychotic depressive reaction were combined to form the psychotic depressives, and those with diagnoses of schizophrenic reaction formed the schizophrenic depressives. There were no significant differences among these three groups on number of male and female patients and on number assigned to the three study medications. The

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psychotic depressives were, however, significantly older than the neurotic and schizophrenic depressives \( (x^2 = 110.1; \ P < 0.01) \). On admission to the study, the psychotic depressives had higher pretreatment scores than the neurotic or schizophrenic depressives in the following areas of psychopathology: depressed mood, hostility, anxiety, cognitive loss, loss of interest in activities, sleep disturbance, and retardation in speech and behavior. Both the psychotic depressives and the schizophrenic depressives had higher pretreatment bizarre thoughts and behavior scores than the neurotic depressives.

The Three Overall Subtypes.—Pretreatment BPRS forms were completed for 549 of the 555 patients included in the study. Based on the degree of similarity of their pretreatment profiles on the BPRS to each of three prototype profiles, patients were classified as either anxious, hostile, or withdrawn-retarded depressives. Sixty-four percent of the sample fell in the anxious depressive group, 21% fell in the hostile depressive group, and 15% were classified as withdrawn-retarded depressives. In the study by Overall et al., anxiety of their patients was classified as anxious depressives. Consequently there was a slightly higher percentage of anxious-depressives in the present study where Overall et al. had a slightly higher percentage of hostile depressives. There were no significant age or sex differences among these three subtypes. In terms of diagnoses, schizophrenics with depression were overrepresented in the withdrawn-retarded group and underrepresented in the anxious depressive group \( (x^2 = 27.47; \ P < 0.01) \).

The Four Age-Sex Groups.—Patients were dichotomized by age into below 40 and 40 years of age and above. Four age-sex groups were then derived: female below 40 (No. = 160), female 40 and above (No. = 206), male below 40 (No. = 61), and male 40 and above (No. = 88). Females comprised approximately 70% of the total sample and patients 40 years of age and above comprised 57% of the total sample. A 2:1 or 3:1 female to male ratio among hospitalized depressed patients has been reported in prior investigations.39,40 As noted previously, there were no significant sex differences among the three diagnostic groups. Psychotic depressives were, however, significantly older and had a wider spectrum of symptoms than the neurotic and schizophrenic depressives.

Statistical Analyses.—A two-way analysis of covariance, controlling for pretreatment symptom scores, was the major statistical approach used to evaluate treatment or main effects and interaction effects (treatment by subgroup). When a covariance F-ratio revealed a significant treatment difference at the 0.05 level or less, a studentized range test was performed to determine where the significant differences were among the three drug treatments.

When a covariance F-ratio revealed a significant interaction effect on the 0.05 level or less, e.g., drug by diagnosis, the final adjusted scores for the three diagnostic groups within each drug treatment were ranked from high (bad) to low (good). In this way, it was possible to determine if there was any consistency in these rankings within each major category of psychopathology and across time. For example, do psychotic depressives on imipramine show consistently lower final adjusted scores on the loss of interest in activity variables than psychotic depressives on either chlorpromazine or a placebo? Is this difference consistent at the various rating periods, i.e., at one, two, three, five, and seven weeks?

Results

Patient Terminations From the Study.—Less than one half, or 40%, of all patients admitted completed the full seven weeks in the study. The major reasons for termination were “clinical course deteriorating,” and “insufficient improvement.” A slightly higher number of placebo than active-drug patients were terminated for these reasons. A higher percentage of patients in the chlorpromazine group were terminated for adverse side effects. The major reasons for side-effect terminations in the chlorpromazine group were skin rash (eight patients) and hypotensive reactions (eight patients).

Significant Drug Differences.—With two exceptions, bizarre thoughts and behavior and denial of illness, the number of significant drug differences within each category of psychopathology exceeded chance expectations based on the number of tests run.

Differences Between the Chlorpromazine and Imipramine Groups.—Differences between the chlorpromazine and imipramine groups will be examined first before turning to differences between the two active treatments and placebo. It will be recalled that study medication was gradually reduced during the patient’s fifth week in the study and patients were off medication entirely during the sixth and seventh weeks. It made sense, therefore, to examine differences separately for these three points in time, i.e., for the first four weeks, for the fifth week, and

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for the sixth and seventh weeks. Table 1 summarizes the number and direction of significant differences between imipramine and chlorpromazine within symptom categories. For example, on one of the variables defining loss of interest in activities was chlorpromazine a significantly better treatment than imipramine during the first four weeks of the study. On the other hand, there were 26 instances during this same treatment period when imipramine was significantly better than chlorpromazine in reducing symptoms of anergia or loss of interest in activities.

The major differences between chlorpromazine and imipramine during the first four weeks of treatment were on loss of interest in activities and retardation in speech and behavior. In both of these categories of psychopathology patients on imipramine showed greater improvement than patients on chlorpromazine. At five weeks, when medication was being reduced, patients on chlorpromazine showed a dramatic spurt in improvement. At this point in time there was only one instance when imipramine was more effective than chlorpromazine in reducing symptoms of anergia and motor retardation. Apparently, the hypokinetic effects of chlorpromazine during the peak dosage phase of the study impeded improvement and, in some instances, may have been responsible for symptoms of anergia and motor retardation. When the drug was removed, patients who had been on chlorpromazine seemed to shrug off their lethargy and to display a greater interest and involvement in hospital activities. Unfortunately, this improvement rate for the chlorpromazine patients was not sustained at six and seven weeks. Instead, there was a marked reduction in improvement with some of these patients showing regression to their pre-five-week symptom levels. In contrast, patients who had been on imipramine continued to show steady improvement at six and seven weeks despite removal of this drug. Differences between the imipramine and chlorpromazine patients at six and seven weeks were apparent in almost all areas of psychopathology but were most pronounced on the depressive mood and cognitive loss variables.

Differences Among the Three Treatment Groups.—During the first four weeks of treatment, both active medications were better than placebo for feelings of guilt and worthlessness, sleep disturbance, excitement, and global severity of illness (Table 2). As compared to chlorpromazine, however, imipramine was more often better than a placebo for depressive mood, hostility, and global change since admission to the hospital. Finally, chlorpromazine was worse than either imipramine or a placebo in reducing symptoms of motor retardation and loss of interest in activities.

At five weeks, when medication was being reduced, chlorpromazine was slightly better than imipramine in reducing hostility and anxiety although both active treatments were better than a placebo. Most of the treatment differences at six and seven weeks were between imipramine and chlorpromazine and these have already been discussed.

How soon do treatment effects occur? There is a general belief that the antidepressants, including imipramine, are slow-acting and that few benefits of these drugs are observed before three weeks. Conversely, the antipsychotic drugs, such as chlorpromazine,
are presumed to be relatively fast-acting. In the present study, however, imipramine looked better than either chlorpromazine or a placebo on the over-all number of beneficial effects at one, two, three, and four weeks.

**Drug by Diagnosis Differences.**—By means of the statistical technique employed in this study, ie, a two-way analysis of covariance, it was possible to extract the main effect on a criterion measure due to drug treatment and any additional or idiosyncratic effect when the drugs were given to various subgroups of depressed patients (interaction effects). From Table 2 it is apparent that drug treatment was the most pervasive factor related to the various outcome measures. In at least four areas of psychopathology—depressed mood, loss of interest in activities, somatic complaints, and excitement—the drug by diagnosis breakdown was, however, helpful in pinpointing the subgroups of depression for whom the active drug treatments and placebo were most or least beneficial.

During the first four weeks of treatment, both placebo and, to a lesser extent, chlorpromazine had an edge over imipramine in the treatment of neurotic depressives (Table 3). At weeks 6 and 7, however, the neurotic depressives who had been on chlorpromazine showed less improvement than the neurotic depressives who had received a placebo during the first five weeks of the study. Further, in one symptom area, loss of interest in activities, placebo was a better treatment during the entire course of the study than either chlorpromazine or imipramine. Neurotic depressives on chlorpromazine also evidenced more agitation and excitement than their counterparts on either imipramine or a placebo.

There were fewer treatment differences among the schizophrenic depressives than among the neurotic or psychotic depressives. For the schizophrenic depressives, however, chlorpromazine was somewhat better than...
Table 3.—Significant Drug by Diagnosis Interactions: No. of High (Bad) and Low (Good) Mean Scores

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Drug*</th>
<th>Wk 1-4</th>
<th>Wk 5</th>
<th>Wk 6-7</th>
<th>Total—Wk 1-7</th>
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<tr>
<td></td>
<td></td>
<td>Good</td>
<td>Bad</td>
<td>Good</td>
<td>Bad</td>
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<td>20</td>
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<td>33</td>
<td>14</td>
<td>2</td>
<td>2</td>
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<tr>
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<td>21</td>
<td>3</td>
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<td>P</td>
<td>8</td>
<td>39</td>
<td>1</td>
<td>5</td>
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<tr>
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<td>29</td>
<td>4</td>
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<td></td>
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<td>P</td>
<td>14</td>
<td>19</td>
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</table>

* C = chlorpromazine; I = imipramine; P = placebo.

either imipramine or a placebo for depressive mood, whereas imipramine was better than chlorpromazine for loss of interest in activities.

As noted in Table 3, imipramine was the preferred treatment for the psychotic depressives. For these patients, imipramine was especially efficacious for depressive mood and loss of interest in activities. In contrast to the neurotic depressives, however, psychotic depressives on imipramine had higher excitement scores than their counterparts on chlorpromazine or a placebo. Both active treatments also resulted in a higher incidence of somatic complaints among these patients than did placebo.

The slump in improvement at six and seven weeks among patients who had been receiving chlorpromazine was most prevalent in the neurotic and psychotic subgroups. In contrast, schizophrenic depressives who had been receiving chlorpromazine showed greater improvement at six and seven weeks than those who had received imipramine or a placebo.

An examination of treatment differences among all drug by diagnosis groups revealed that, in general, the psychotic depressives on either chlorpromazine or a placebo showed the poorest over-all response. Conversely, the neurotic depressives on either chlorpromazine, imipramine, or a placebo and the psychotic depressives on imipramine showed the most favorable treatment response over time and across rating instruments.

Treatment Differences Among the three Overall Depression Subtypes.—The analyses of differential drug effects among anxious, hostile, and withdrawn-retarded depressives were quite disappointing. Of the 1,000 tests run only 49, or 5%, of the drug by Overall subtype interactions were statistically significant. Within these three subtypes of depression there were, however, some interesting differences in drug effectiveness at various points in time (Table 4). With the exception of week five, when medication was being reduced, imipramine was the best treatment for the anxious depressives. For the withdrawn-retarded depressives, imipramine was best during the first four weeks of treatment. At weeks six and seven, after medication was discontinued, there was an interesting reversal with withdrawn-retarded patients who had been on placebo showing the greatest improvement and those on imipramine showing the least improvement from their pretreatment levels. Hostile depressives did best on a placebo during the first four weeks of treatment but, by the sixth and seventh week in the study, the hostile depressives who had been on imipramine showed the greatest overall improvement. The meaning of these findings is not entirely clear. Possibly imipramine is a useful agent for controlling the symptoms of depression in the withdrawn-retarded patients and when the drug is withdrawn the symptoms reappear. Placebo may also be a beneficial treatment for the hostile depressives who react adversely when the placebo capsule is withdrawn. Obviously, these “explanations” require further investigation.

Treatment Differences Among the Age-Sex Groups.—Although the total number of significant interactions involving drug and age-sex was small, the direction of the drug differences within each age-sex group were consistent, especially for the female patients (Table 5). Female patients under 40 showed a good response to placebo and a poor response to imipramine, whereas those 40 and older showed a good response to imipramine and a poor response to both chlorpromazine and a placebo. These differences were most pronounced on the depressive mood, hostility,
and cognitive loss and subjective uncertainty variables. In contrast to the female patients, male patients under 40 did poorly on placebo and well on the active treatments. Males 40 and over responded best to imipramine. Consequently, both male and female patients 40 and over did well on imipramine but females under 40 were helped most by placebo whereas males under 40 were helped most by the two active treatments.

Comment

To a surprising extent, study findings were consistent with current clinical impressions surrounding the use of imipramine and chlorpromazine in depression. Imipramine appeared to have mild euphoriant or energizing effects as this drug was useful in countering symptoms of depressive mood and anergia. These effects would also account for the higher agitation and excitement scores among some psychotic depressives who received imipramine. Imipramine was also surprisingly effective for sleep disturbance and in reducing symptoms of anxiety and feelings of guilt and worthlessness. On the basis of their behavioral effects and action at receptor sites, Dewhurst\textsuperscript{31} has noted that certain amines have a biphasic action with associated euphoriant and depressant effects. Imipramine or its metabolites may fall into this category.

Imipramine was most useful for psychotic depressives and for patients 40 years of age or older. If, as reported, there is a relationship between endogenous depression and psychotic depression then these results are consistent with the findings of Kiloh et al\textsuperscript{12} and others\textsuperscript{3-11} that imipramine is especially beneficial in endogenous depression. Further, as reported by Kiloh et al.,\textsuperscript{12} this drug was not very effective for neurotic depressives. Imipramine was also a poorer treatment than a placebo for female patients under 40. Wittenborn\textsuperscript{13} had previously reported that female patients under 45 with paranoid symptoms failed to respond to imipramine.

Despite some recent evidence that a major tranquilizer was effective for anxious or agitated depressives,\textsuperscript{9,33} there is a persistent belief that these drugs are not very effective in the treatment of depression. With few exceptions, study findings tended to support this belief. In general, imipramine rather than chlorpromazine was the preferred treatment for depression. Further, the hypokinetic effects of chlorpromazine made this drug less beneficial than either imipramine or a placebo for symptoms of anergia and motor retardation. Chlorpromazine was effective, however, in reducing symptoms.
of agitation and excitement among the psychotic depressives. Consequently, if a depressed patient is extremely agitated or excited, there may be some advantage in combination treatment, i.e., combining an antidepressant with a tranquilizer.

There is also a prevalent belief, supported by a number of controlled studies, that the antidepressants, including imipramine, are not very effective in the treatment of depression. To some extent, study findings were also consistent with this belief. Although imipramine did have beneficial effects, these effects were generally small and did not apply to all patients. With 555 patients, small differences among treatments were often statistically significant. For example, when a treatment difference was significant, the amount of variance in the outcome measure associated with drug treatment was calculated. These variance estimates ranged from 2% to 10%. In other words, at best, drug treatment accounted for 10% of the variance associated with a particular outcome or criterion measure. With a smaller sample size, as was the case with all of the previous controlled trials of imipramine in depression, many of the treatment differences in the present study would have failed to reach a statistically significant level.

The comment was made that imipramine was not beneficial for all depressed patients. First, approximately 25% of the patients started on either imipramine or chlorpromazine were dropped during the active treatment phase of the study, i.e., during the first five weeks, for insufficient improvement or deteriorating mental condition. Secondly, the breakdown of patients into various subgroups revealed that neurotic depressives showed the greatest improvement over time and for these patients placebo was as effective as the active treatments. Placebo was particularly good for female patients under 40 years of age. Finally, there was little evidence to recommend either imipramine or chlorpromazine for the schizophrenic depressives.

In the preceding paragraph, the point was made that, at best, drug effect accounted for 10% of the variance associated with a particular outcome measure. Variance estimates were also computed for the effects of diagnosis, the three Overall subtypes, and age-sex on outcome. Again, at best, each of these sets of variables accounted for approximately 10% of the variance associated with a specific outcome measure. Correlations between pretreatment and posttreatment symptom scores were generally in the mid 30%, so that pretreatment score also accounted for roughly 10% of the variance in outcome. These are not independent or unrelated variables, however, and it would be surprising if the net effect of drug, diagnosis, Overall subtype, age-sex, and pretreatment symptom score accounted for more than 50% of the variance in the various criterion measures. Consequently, although some progress has been made toward understanding the factors related to symptom reduction or improvement in hospitalized depressives, a major share of the predictable variance in these outcome measures remains unexplained. Recently, Galbrecht and Klett failed to replicate predictive equations for predicting the right drug for the right patient in newly hospitalized schizophrenics. These investigators, however, relied solely on symptom rating scale measures as their predictors. To enhance prediction of outcome among schizophrenics they suggested the inclusion of social and psychiatric history variables. This suggestion also has merit for depressives. Conceivably, the inclusion of premorbid competence, social, and psychiatric history variables would further reduce the unexplained variance in the outcome measures in the present study and permit more intelligent judgments regarding drug assignment and prognosis among the heterogeneous sample of psychiatric patients who enter a hospital with depression as a major feature of their illness.

Summary

Chlorpromazine, imipramine, and a placebo were administered double-blind to 555 depressed patients from ten collaborating hospitals. Major evaluations of clinical status were made prior to drug assignment and again at the end of one, two, three, five, and seven weeks in the study. The medication schedule called for peak dosages of study medication from the second through the fourth week in the study. Medication was gradually reduced during the fifth week and
discontinued entirely during the sixth and seventh weeks. The median daily dosages were 300 mg of imipramine and 600 mg of chlorpromazine. With pretreatment symptom scores covaried out, tests were made of simple drug differences and of differential drug effects among various depressive subgroups.

During the first four weeks of treatment, both active treatments, ie, imipramine and chlorpromazine, were better than a placebo for feelings of guilt and worthlessness, sleep disturbance, excitement, and global severity of illness. During this same time period, however, imipramine was significantly better than chlorpromazine for symptoms of anergia and motor retardation. Imipramine also appeared to be a better treatment than chlorpromazine for depressed mood.

At week five, when medication was being reduced, the chlorpromazine patients showed a dramatic spurt in improvement, particularly on the anergia and motor retardation variables. At week seven, however, two weeks after medication was discontinued, the patients who had been on imipramine showed greater over-all improvement in almost all areas of psychopathology than patients who had received chlorpromazine.

In general, placebo was as effective as imipramine or chlorpromazine for the neurotic depressives. Imipramine was, however, the preferred treatment for psychotic depressives, especially for symptoms of depressed mood and anergia. There were few significant treatment differences among the schizophrenic depressives.

The analyses of different drug effects among the three Overall depressive subtypes revealed few significant differences. During the first four weeks of treatment imipramine had a slight edge over chlorpromazine or a placebo for both the anxious and withdrawn-retarded depressives. During this same time period hostile depressives did best on a placebo.

Both male and female patients 40 and over did well on imipramine but females under 40 were helped most by placebo, whereas males under 40 were helped most by the two active treatments.

Although there were many statistically significant treatment differences on the outcome measures, these differences were generally small. Further, at best, treatment differences accounted for only 10% of the predictable variance on any outcome measured. Consequently, for many depressed patients, drugs play a minor role in influencing the clinical course of their illness.

Tables A through D containing the results (final adjusted means and F-ratio’s) of two-way covariance analyses which revealed significant drug and drug by patient subgroup interactions in clinical effects can be obtained from Dr. Raskin.

This is a report of the second of three major studies by the National Institute of Mental Health, Psychopharmacology Research Branch (PRB), Collaborative Depression Study Group. Data were contributed by the following investigators and their staffs from ten collaborating hospitals: Charles Avery, MD, Hartford, Conn; Alberto DiMascio, PhD, Boston; Robert W. Downing, PhD, Philadelphia; Glen M. Duncan, MD, Rochester, Minn; Harold Feldman, MD, Rochester, NY; Alfred S. Friedman, PhD, Philadelphia; Robert W. Gibson, MD, Towson, Md; George L. Hall, MD, Washington, DC; Pedro J. Irigoyen, MD, Butner, NC; Kathleen Smith, MD, St. Louis. These investigators and their research staffs also took an active part in the planning phases of this study. The research was under the overall direction of Jonathan O. Cole, formerly Chief of the PRB and now Superintendent of Boston State Hospital, and Solomon C. Goldberg, Assistant Chief of the PRB.

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The drugs used in the study were donated by Smith, Kline, & French (chlorpromazine) and Geigy (imipramine).

Nonproprietary and Trade Names of Drugs

Thioridazine—Mellaril.
Chlorpromazine—Thorazine.
Imipramine—Tofranil.

References


6. Delay J, Deniker F: Efficacy of Tofranil in the treatment of various types of depression: A compari-
15. Wittenborn JR: Prediction of the individual's response to antidepressant medication. Read before the meeting of the American College of Neuropsychopharmacology, San Juan, Puerto Rico, 1965.
Reliability. Internal consistency for the Depression scale was found to be .95 in two separate studies. Test–retest reliability of the Depression scale was estimated to be .74 in one study that included 100 patients entering treatment at a university-based psychiatry center.

Validity. The POMS Depression scale was found to correlate highly with other measures of depressive symptomatology. For example, the $r$ value regarding its association with the BDI (p. 29) and MMPI-D scale (p. 73) was found to be .61 and .65, respectively.

Clinical Utility

High. The POMS has been used extensively to assess overall emotional distress in many investigations. It is likely, however, to be less sensitive and precise with regard to assessing depressive symptomatology as compared to measures designed solely for that purpose.

Research Applicability

High. The POMS has been used extensively in a variety of research studies.

Resource

EdITS, P.O. Box 7234, San Diego, CA 92167. Phone: 800-416-1666.

Cost

$9.00 for the manual and one copy of all forms (long and short forms); $9.50 for a package of 25 POMS inventories.

Alternative Forms

A short-form exists.

RASKIN THREE-AREA SEVERITY OF DEPRESSION SCALE

Original Citation

Purpose

To rate the severity of depressive symptoms in three general areas: verbal report, behavior, and secondary symptoms.

Population

Depressed adults in inpatient and outpatient settings.

Description

The Raskin Three-Area Scale is a three-item clinician-rated instrument that measures the severity of patients' depressive symptoms in the global areas of verbal report, behavior, and secondary symptoms of depression. Examples of symptoms are provided for the clinician in each area of depressive symptomatology (e.g., "Says he feels blue and talks of feeling helpless or worthless" is provided as an example of verbal report). Each of the three areas is rated along a 5-point scale ranging from 5 to 1 which represent descending severity of depressive symptoms.

Background

The Raskin Three-Area Scale was developed to provide a method for determining inclusion in a study examining the differential responses of depressed individuals to chlorpromazine, imipramine, and a placebo. Inpatients with a score of 9 or greater were determined to have at least moderate levels of depression and were included in the study. Later studies, which examined drug effects on outpatients, lowered the score for inclusion to 7.

Administration

Clinicians rate the severity of symptoms based on their observations of patient behavior and the cues provided for each area of depressive symptomatology; the instrument requires approximately 30 minutes.

Scoring

One simply adds the score for each of the three items in order to produce a total score. Scores range from 3 to 15.
**Interpretation**

A cutoff score of 9 has typically been used as the criterion for including inpatients in studies of psychopharmacological treatment effects; a cutoff score of 7 has been used for outpatients.

**Psychometric Properties**

**Norms.** Not applicable.

**Reliability.** Data on the reliability of the Raskin Three Area Scale are limited. According to Raskin (as cited in Bellack & Hersen, 1988), intraclass reliability coefficients developed from 880 depressed inpatients, 94 depressed outpatients, and 239 depressed patients in private practice were all in the high 80s.

**Validity.** Similar to the reliability data, validity data on this instrument are also limited.

**Clinical Utility**

Limited. This instrument was developed to determine inclusion in drug trials. It was not intended for clinical use, and has not been tested for this purpose.

**Research Applicability**

Limited. Studies have shown that this instrument is a reliable screening instrument for entry into drug trials. According to Raskin (as cited in Bellack and Hersen, 1988), some studies have shown that this scale is sensitive to treatment effects. Although some studies have also used the Raskin Three-Area Scale as an outcome measure, the test was not developed for this purpose and its reliability and validity have not been examined in this capacity.

**Source**

The Raskin Three-Area Scale is reprinted in Appendix B. For additional information, contact Dr. Allen Raskin, Department of Psychiatry, University of Maryland School of Medicine, 645 West Redwood Street, Baltimore, MD 21201.

**Cost**

None.

**Alternative Forms**

None.
### Raskin Three-Area Severity of Depression Scale

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**Severity of Depression:** To what extent does the individual evidence depression or despondency in verbal report, behavior, and secondary symptoms of depression?

<table>
<thead>
<tr>
<th>Cues</th>
<th>Very Much</th>
<th>Considerably</th>
<th>Moderately</th>
<th>Somewhat</th>
<th>Not At All</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Verbal Report</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Says he feels blue; talks of feeling helpless, or worthless; complains of loss of interest; may wish he were dead; reports crying spells</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td><strong>Behavior</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Looks sad; cries easily; speaks in a sad voice; appears slowed down; lacking in energy.</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td><strong>Secondary Symptoms of Depression</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia, G.I. complaints; dry mouth; history of recent suicide attempt; lack of appetite; difficulty concentrating or remembering</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Add the scale points checked for severity of depression in verbal report, behavior and secondary symptoms of depression</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TOTAL:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# SEVERITY OF DEPRESSION AND MANIA SCALE

**RAISIN 3-area scale**

**DEPRESSION**

To what extent does the subject evidence depression or despondency in verbal report, behavior, and other symptoms of depression?

<table>
<thead>
<tr>
<th></th>
<th>Very much</th>
<th>Considerable</th>
<th>Moderately</th>
<th>Somewhat</th>
<th>Not at all</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VERBAL REPORT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Says he feels blue; talks of feeling helpless, hopeless or worthless; complains of loss of interest; may wish he were dead; reports crying spells.</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td><strong>BEHAVIOR</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Looks sad; cries easily; speaks in a sad voice; appears slowed down; lacking in energy.</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td><strong>SECONDARY SYMPTOMS OF DEPRESSION</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia; G.I. complaints; dry mouth; history of recent suicide attempt; lack of appetite; difficulty concentrating or remembering.</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

**TOTAL**

Add the scale points checked for severity of depression in verbal report, behavior and secondary symptoms of depression.

---

**MANIA**

To what extent does the subject evidence manic behavior in verbal report, behavior, and other symptoms of mania?

<table>
<thead>
<tr>
<th></th>
<th>Very much</th>
<th>Considerable</th>
<th>Moderately</th>
<th>Somewhat</th>
<th>Not at all</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VERBAL REPORT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Says he feels high, elated, great, on top of the world, optimistic; expresses expansive mood (may be irritable when restrained), inappropriate self confidence, grandiosity.</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td><strong>BEHAVIOR</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Looks gay or elated; jokes; loud voice; garrulous, seductive behavior; psychomotor excitement.</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td><strong>OTHER SYMPTOMS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Needs less sleep than usual, thoughts racing, increased energy, increased activity level, hypersexuality, inappropriate behavior, poor judgment.</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

**TOTAL**

Add the scale points checked for severity of mania in verbal report, behavior, and other symptoms.