Journal of Affective Disorders, 17 (1989) 99–104
Elsevier

JAD 00633

Treatment of adolescents with major depression: implications of the DST and the melancholic clinical subtype

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(Received 18 April 1988)
(Accepted 14 December 1988)

Summary

Of 38 adolescents hospitalized with major depression, 47% of those receiving psychosocial treatment alone responded. Of the non-responders then treated with combined tricyclic antidepressants and psychosocial treatment, 92% responded. The melancholic subtype and dexamethasone suppression test non-suppression were associated with failure to respond to psychosocial treatment alone. Implications for controlled studies are discussed.

Key words: Depression; Adolescence; Tricyclic antidepressants; Dexamethasone suppression test; Melancholia

Introduction

No controlled studies have demonstrated efficacy of any modality for the treatment of major depression (MD) in adolescents. The only controlled study of tricyclic antidepressants (TCA) reported no difference between amitriptyline and placebo, but was limited by a small sample, lack of an initial drug-free phase, and ambiguous criteria for diagnosis and improvement (Kramer and Feiguine, 1983), and an uncontrolled trial of imipramine in outpatients reported improvement of only 44% (Ryan et al., 1986). Similarly, no controlled studies of psychosocial modalities, such as cognitive and interpersonal therapies, have been reported in adolescents. Observed similarities between juvenile and adult forms of affective disorder in phenomenology (Kandell and Davies, 1986), incidence of dexamethasone suppression test (DST) non-suppression (Robbins et al., 1983; Preskorn et al., 1987) and family history (Kovacs and Paulauskas, 1984), however, suggest that treatment response may also follow patterns seen in adults.

The identification of clinical subtypes may be important in the design and evaluation of clinical trials, for associations between subtypes and response to psychosocial or somatic treatment have been seen in adults. The failure to make such

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distinctions in the design of a study could lead to the test of a treatment in a population including subgroups in which the response rate could be expected to be low with the consequent minimization of significant treatment effects.

Certain subtype distinctions have appeared to be associated with treatment response in adult populations. The endogenous or melancholic subtype is associated with greater response to tricyclic antidepressants than to psychosocial therapies (Prusoff et al., 1980; Nelson et al., 1984). Delusional patients (Spiker et al., 1985), bipolar patients in an episode of depression (Himmelhoch et al., 1972), and 'atypical' depressives (Klein et al., 1980) are other phenomenologic subtypes for which evidence exists in adult populations suggesting different treatment needs. Other subgroups may also have particular patterns of treatment responsiveness, such as those in whom comorbidity exists with panic disorder or dysthymia. It appears plausible that biological as well as clinical indicators might exist of the need for and response to somatic treatments, but despite considerable effort, such profiles remain elusive. DST non-suppression has been reported to be associated with failure to respond to placebo in two studies of adults (Peselow et al., 1986; Brown et al., 1987) and in one of prepubertal children (Preskorn et al., 1987). A study of cognitive therapy in adult outpatients reported an association of non-suppression with poor response (Rush, 1982).

This paper reports naturalistic, uncontrolled clinical experience of the treatment of adolescents hospitalized with MD. It describes the association of response to psychosocial treatment alone and combined with tricyclic antidepressants with the melancholic and non-melancholic subtypes and with DST non-suppression.

Method

As part of a study of the sensitivity and specificity of the DST in adolescence, psychiatric inpatients were interviewed using the Schedule for Affective Disorders and Schizophrenia (SADS) by two child psychiatrists, and a DSM-III diagnosis was assigned. The reliability and validity of criteria-based diagnoses in adolescents, based on semi-structured interviews, has been described elsewhere (Strober et al., 1981; Robbins et al., 1982). It should be noted that all those meeting criteria for MD were significantly incapacitated by their symptoms, and generally exceeded by weeks to months the requirement for 2-week duration. No patients had significant medical illness. Mean age was 15.6 years; age range was 13–17. All were free of psychotropic medications at least 2 weeks prior to the DST. Consenting patients were given a 1 mg DST with blood samples at 11:00 p.m. on day 1; and at 8:00 a.m., 4:00 p.m., and 11:00 p.m. on day 2. Cortisol assays were done by competitive protein binding (Ritchie et al., 1985). Exclusion criteria for the DST and results of the DST study have been reported elsewhere (Robbins et al., 1983). DST results were kept blind until diagnoses were assigned. Since the SADS and DST were part of a study of diagnosis and DST, not including formal study of treatment response, DST results were known to the attending psychiatrist 2 weeks after admission. Neither subsequent treatment decisions nor assessment of response were blind to diagnostic subtype or DST results. This report describes the uncontrolled treatment experience with depressed adolescents included in the study of the DST and initial diagnosis.

Adolescents meeting criteria for MD received intensive psychosocial treatment alone for at least 6 weeks, consisting of psychodynamically oriented interpersonal individual psychotherapy three times per week, family therapy weekly, group therapy twice weekly, and an active cognitive-behavioral therapeutic milieu. Psychotherapy emphasized current relationship difficulties, particularly between the adolescent and his or her immediate family and peers. Specific traumatic events or relationships were addressed, but early experience, intrapsychic material, and regressive transferences were not emphasized. While a specific therapy manual was not used, the approach was similar to that described as interpersonal psychotherapy (Klerman et al., 1984). The activities of the inpatient program attempted to reflect common experiences of an adolescent's daily life – e.g., school, chores, social interactions, dealing with authority figures – with regulation by staff to create experiences of oneself as effective and worthwhile and of the world and future as positive. The milieu,

then, integrated elements of interpersonal and cognitive-behavioral approaches. Though impure from a research perspective, this approach to psychosocial treatment is not unusual in the treatment of adolescents, and may add to the generalizability of these observations. A trial of TCA was considered for those who failed to respond as judged by their attending psychiatrist as having persisting depression or anhedonia equivalent to SADS item ratings of 3 or more. Active psychosocial treatment was continued during TCA treatment. Since the relationship of response to dose or plasma level is not established in adolescents, dosage was selected to achieve blood levels reported as efficacious in adults within 2 weeks or less, e.g., for desipramine, 150–225 ng/ml imipramine plus desipramine. Patients were considered to have had an adequate trial if they remained at such levels for 4 weeks. Improvement was based on the judgement by the attending physician (M.V.C. or D.R.R.) equivalent to a SADS item rating of 1 ('not at all') or 2 ('slight') for the depression and anhedonia items.

Results

Of 81 patients admitted who consented to a SADS interview and a DST, 38 met DSM-III criteria for MD. Data on the association of the DST and diagnosis have been previously reported (Robbins et al., 1983). Of the 38, 23 received psychosocial treatment alone, only 15 received TCA with continued psychosocial treatment.

Eighteen of the 38 patients (47%) responded to psychosocial treatment alone. Of 19 non-melancholic (Non-Mel) patients, 13 responded without medication (68%), while of 19 melancholic (Mel) patients only five responded without medication (26%) (χ^2, Yates correction = 5.17, $P < 0.05$, $df = 1$) (Table 1). Eighteen of 31 (58%) DST suppressors and no non-suppressors improved with intensive psychosocial interventions without medications (χ^2, Yates correction = 4.56, $P < 0.05$, $df = 1$) (Table 2). All patients who responded to psychosocial treatment alone were DST suppressors. Five suppressors failed to respond to psychosocial treatment alone, but did not receive TCA because of refusal by the patient or family. All seven non-suppressors failed to respond to psychosocial treatment alone and went on to TCA trials.

TABLE 1

MELANCHOLIC SUBTYPE AND RESPONSE TO PSYCHOSOCIAL TREATMENT ALONE

	Melancholic	Non-melancholic	Total
Responders	5	13	18
Non-responders	14	6	20

Chi square, Yates correction = 5.17, $P < 0.05$, $df = 1$.

Fifteen patients who failed to respond to psychosocial treatment alone were given trials of TCA: 10 with desipramine alone, two with imipramine, one with amitriptyline alone, one with nortriptyline, and one first with desipramine and then with amitriptyline. Of these, three had trials interrupted by adverse reactions — two because of hypomania, and one because of persistent orthostatic hypotension on desipramine and acute urinary retention on amitriptyline. Of the 12 completing trials, 11 (92%) has positive responses to TCA alone. One developed hypomania on desipramine, had a recurrence of depression on lithium, but did well on desipramine and lithium. All five Non-Mel patients responded to TCA (Table 3). Six of seven Mel patients (86%) responded to TCA alone; one responded to desipramine and lithium. All DST suppressors and five of six non-suppressors responded to tricyclic alone with one non-suppressor responding to desipramine and lithium (Table 4).

Of those who received adequate trials of TCA or TCA and lithium, essentially all improved markedly with respect to the core symptoms of major depression, depressed mood and anhedonia, so medication response was not associated with

TABLE 2

DEXAMETHASONE SUPPRESSION AND RESPONSE TO PSYCHOSOCIAL TREATMENT ALONE

	DST non-suppression	DST suppression	Total
Responders	0	18	18
Non-responders	7	13	20

Chi square, Yates correction = 4.56, $P < 0.05$, $df = 1$.

TABLE 3

NON-RESPONDERS TO PSYCHOSOCIAL TREATMENT ALONE: MELANCHOLIC SUBTYPE AND RESPONSE TO MEDICATION PLUS PSYCHOSOCIAL TREATMENT

	Melancholic	Non-melancholic	Total
Responders to TCA alone	6	5	11
Responders to TCA/Li	1	0	1
Non-responders	0	0	0
Inadequate trials	3	0	3

TCA, tricyclic antidepressant; TCA/Li, tricyclic antidepressant plus lithium carbonate.

DST results or diagnostic subtype. In some of the adolescents, behavioral symptoms, e.g., running away, or cognitive symptoms such as poor self-esteem or pessimism persisted. This is consistent with the differential effect reported in adults of tricyclic antidepressants on 'vegetative' symptoms, with later, perhaps independent improvement in cognitive constructs and social function (Weissman et al., 1974; DiMascio et al., 1979; Rush, 1982; Simons et al., 1984). The clinical impression was that in a minority of these patients improvement in depression was associated with a global improvement in all symptoms, while in the majority such symptoms as conduct disorder, provocative behavior within the family, or disturbance of self-perception persisted but became more accessible to psychosocial approaches.

Discussion

The observation that approximately half of a sample of adolescents hospitalized for major depression improved without medication while others required somatic treatment suggests the heterogeneous nature of the DSM-III diagnostic category of major depression. Despite having symptoms severe enough to require hospitalization, a large subgroup experienced improvement after the beginning of family and individual psychotherapy and a move from home to the inpatient milieu, while others remained depressed until medication was added. Such a high apparent response to psychosocial treatment of major depression, particularly in the Non-Mel and DST-suppressing subgroups, deserves further study. We cannot know how many remitted spontaneously, unrelated to treatment, although most had been symptomatic for weeks or months and improved within the first 4 weeks of hospitalization. This is consistent with the finding of a high (68%) placebo response rate in a study of prepubertal depression (Puig-Antich et al., 1987). The only controlled study of a TCA in adolescents (Kramer and Feiguine, 1983), began medication after a 2-day 'adjustment period', and then found high rates of improvement in both placebo- and amitriptyline-treated groups with no difference between groups. Conceivably, both groups included many patients who would have responded without medication.

The distinction of Mel and Non-Mel clinical subtypes appears to be meaningful. Of the Non-

TABLE 4

NON-RESPONDERS TO PSYCHOSOCIAL TREATMENT ALONE: DEXAMETHASONE SUPPRESSION AND RESPONSE TO MEDICATION PLUS PSYCHOSOCIAL TREATMENT

	DST non-suppression	DST suppression	Total
Responders to TCA alone	6	5	11
Responders to TCA/Li	1	0	1
Non-responders	0	0	0
Inadequate trials	3	0	3

TCA, tricyclic antidepressant; TCA/Li, tricyclic antidepressant plus lithium carbonate.

Mel group, 68% were successfully treated without medication, while of the Mel patients treated without medication only 26% appeared to improve. Of those non-responders to psychosocial treatment who were given medications, both subtypes improved equally.

DST non-suppression appeared to be associated with a failure to respond to psychosocial treatment alone, or a need for somatic treatment. Despite the program's approach of giving patients weeks to months to respond to psychosocial interventions, it appears noteworthy that all those with DST non-suppression eventually were considered to require medication.

These observations are limited by several factors. Treatment assignment and judgements of efficacy were not blind to clinical subtype or DST results, and may have been biased. Specific protocols for tricyclic administration and psychosocial treatment were not used. Judgements of efficacy focused on depressed mood and anhedonia and did not include other symptoms known to respond to treatment. Placebo control groups were not used. Unfortunately, systematic data on additional variables of possible importance, such as family psychiatric history or comorbidity with substance abuse, conduct disorder, or personality disorder, are not available.

This clinical report suggests methodological issues for prospective, controlled studies. A medication-free interval after hospitalization of at least 2 weeks appears important to identify patients who improve without medication. DST or other biological study results should remain blind throughout the trials. Psychosocial interventions need to be either controlled or at least specified (e.g., cognitive, interpersonal). Diagnoses and response need to be defined by specific criteria. The Mel–Non-Mel distinction appears important, and an analysis of specific symptoms within the Mel constellations – e.g., psychomotor retardation, diurnal variation – may yield a more specific profile of the depressed adolescent who requires and responds to TCA. The degree and timing of the responses of specific symptoms to both psychosocial and pharmacological treatment should be defined. The DST appears to deserve study as an indicator of the need for somatic treatment and deserves further study, as does the observation that many patients continue to have serious behavioral, family, and cognitive disturbances following the resolution of their depressive symptoms. Controlled, more specific observations may help us to prescribe both psychosocial and somatic therapies more precisely. Beyond both clinical applications and the implications for the adolescent population, the relationships among clinical characteristics, biological correlates, and treatment response may allow us to dissect the heterogeneous phenomenon of major depression into subtypes more meaningfully related to underlying mechanisms.

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