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Trait anxiety and the effect of a single high dose of diazepam in unipolar depression

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Abstract

In this cross-sectional study we explored in 101 depressive in-patients (DSM III-R) the association between level of trait anxiety and variables that have been investigated previously to discern primary and secondary depression, respectively. Besides, we explored the influence of trait anxiety level on difference in treatment response to either imipramine or mirtazapine. Trait anxiety was measured interviewing a close relative of the patient using a questionnaire related to aspects of psychic anxiety and to aspects of somatic anxiety. The interviewer focussed on fluctuating anxiety symptoms without persistent mood disturbance during the patient's normal lifelong functioning before developing a depressed mood. We found no relation between trait anxiety level and treatment response to either imipramine or mirtazapine. The most important finding of this study is the significant differential response to the diazepam test: depressive patients with high trait anxiety showed, predominantly, a disappearance of depressive symptoms without sedation and depressive patients with low trait anxiety showed, predominantly, sedation without disappearance of depressive symptoms. The opposite response to the diazepam test in patients with a different history of trait anxiety in spite of similar depressive symptomatology suggests differences in underlying pathophysiologic mechanisms.

Keywords: Depression; Trait Anxiety; Diazepam test; MAO activity; Neuroticism; Treatment response

1. Introduction

Patients with a history of anxiety often develop depression later in their life. This applies to anxiety disorders (Clancy et al., 1978; Dealy et al., 1981; Schatzberg et al., 1990; Moras and Barlow, 1992) proper as well as to chronic anxiety symptoms not fulfilling the diagnostic criteria for anxiety disorder. Van Valkenburg et al. (1983) e.g. found differences between depressive patients with chronic lifelong nervousness preceding the onset of depression (anxiety as a trait, without having a diagnosable preceding anxiety disorder) and patients without this premorbid nervousness.

The concept of depression secondary to chronic anxiety may be related to the "psychasthenia" concept of Janet (Jelgersma, 1939): in addition to patients with melancholia (primary depression) he observed patients who had a lifelong vulnerability, a trait, to develop various complaints such as phobias, compulsions, doubt, shame, fear for the future, depersonalisation and fatigue. A related concept was proposed by Akiskal (1998): "Generalised anxious temperament" (GAT) with lifelong high trait anxiety which fluctuates in reaction to stress and which can escalate to a full-blown generalised anxiety disorder. According to Akiskal, Generalised anxiety disorder (GAD) is in continuum with GAT. Generalised anxiety temperament may predispose to and is often associated with depression. The view of generalised anxiety being a personality trait which can exacerbate into an anxiety disorder and which predisposes to depression is in line with the evidence from longitudinal studies that chronic anxiety disorders are not infrequently accompanied by secondary depression, whereas chronic depression is rarely associated with a secondary anxiety disorder (Cloninger et al., 1981).

Nuller et al. (1982) reported that the reaction to the diazepam test distinguished primary depressions from depressions secondary to anxiety and predicted a good response to treatment with an antidepressant or to treatment with a benzodiazepine, respectively.

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We performed a cross-sectional study in depressed patients exploring clinical, personality and biological variables, which could give more insight into the differences between patients with a low level of trait anxiety and patients with a high level of trait anxiety.

In imitation of the trait anxiety concepts of Van Valkenburg et al. (1983), Janet (Jelgersma, 1939) and Akiskal (1998) we defined trait anxiety as a lifelong disposition to develop (too) easily various symptoms of psychic and somatic anxiety in reaction to stressful circumstances which fluctuate in time and which sometimes can escalate to a full-blown anxiety disorder.

2. Material and methods

The study was performed on the in-patient depression unit of the Department of Psychiatry of the University Hospital "Dijkzigt" Rotterdam. Eligible patients had to be drugfree for at least 3 days before baseline assessment. *Included* were patients aged 18–65 with a "major depressive episode" [DSM-III-R (American Psychiatric Association, 1987)] with a Hamilton Rating Scale for Depression (HRSD) $^{3}18$ (Hamilton, 1960). *Excluded* were patients with schizophrenia, paranoid psychosis, organic brain syndrome, chronic drug or alcohol abuse, clinically relevant renal, hepatic, cardiovascular, or endocrine disease, presence of absolute contraindication for either imipramine or mirtazapine, and pregnancy or the risk to become pregnant. Patients were given a detailed outline of the study, following which, written informed consent was obtained and a single blind placebo was administered for 4 days.

The variables to be examined because of their possible relationship with trait anxiety were neuroticism (Stavrakaki and Vargo 1986), MAO activity in platelets (Davidson et al., 1980), response to a single high dose of diazepam [diazepam test (Nuller et al., 1982)] and response to treatment.

At the end of the placebo period, thus after a period of at least 7 days free of active medication, MAO activity in platelets was measured, a provocation test with diazepam was performed, and subsequently, patients were randomly allocated to double-blind treatment with either imipramine or mirtazapine. Doses of both drugs were adjusted to obtain fixed plasma levels as described previously (Bruijn et al., 1996). Outcome measurement with the HRSD was performed 4 weeks after attaining this predefined adequate blood level. Response was defined a priori as a reduction of 50% or more of the outcome HRSD-score.

All assessments were done by one research psychiatrist (J.B), except the section of the Schedule for Affective Disorders and Schizophrenia [SADS, (Spitzer and Endicott, 1981)], which relates to depression, which was performed in the presence of a second psychiatrist. This standardised interview was administered before the start of the placebo period to obtain RDC-diagnoses (Spitzer et al., 1978) and to assess state anxiety symptoms. Scoring was based on consensus between both psychiatrists. During the baseline period there was an interview with the partner or a first-degree relative of the patient to evaluate the patient's history of possible anxiety disorders, administering a questionnaire, which comprised the SADS-questions on anxiety disorders (to identify patients with a history of anxiety disorders) and to assess the level of trait anxiety using a questionnaire with questions pertaining to trait anxiety. This interview was not performed with the patient himself to minimise the risk of the trait anxiety score being biased by state anxiety symptoms in these severely depressed patients. The interviewer focussed on fluctuating anxiety symptoms without persistent mood disturbance and asked the referee empathically to base the answers on the patient's normal lifelong functioning before developing a depressed mood. Because Spielberger's (1970) well known and validated State-Trait Anxiety Inventory (STAI) seems to be based on a more restricted trait anxiety concept than as it is defined in the present study and because this inventory is not suited to interviewing a relative of the patient, we composed a questionnaire ourselves. The 34 questions of this questionnaire were both related to aspects of psychic anxiety and to aspects of somatic anxiety (Table 1). Both presence, intensity and frequency of items were quantified (score of each question: 0–4 i.e. absent, mild, moderate, severe; range of total score: 0–136).

MAO activity (μmol/l×hour) was measured in whole blood with kynuramine as the substrate (Van Kempen et al., 1985) and calculated per platelet. The diazepam test was applied according to Nuller et al. (1982) by

Table 1
Items of the 34 questions pertaining to trait anxiety

Psychic anxiety	Somatic anxiety
Tension	Restlessness
Nervousness	Trembling
Anxious feelings	Muscle tension
Worrying about the future	Muscle ache
Worrying about the health of one's kin	Insomnia
Fear of dying	Shortness of breath
Fear of going crazy	Chest pain
Fear of losing control	Choking
Inability to relax	Palpitations
Irritability	Dry mouth
Impatience	Abdominal distress
Concentration disturbances	Diarrhoea
Depersonalisation	Frequent urination
Indecisiveness	Dizziness
Uncertainty	Sweating
Hypochondriasis	Tingling in hands or fingers
	Faintness
	Fatigability