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REVIEW

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Neuroleptic dysphoria: towards a new synthesis

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Abstract *Rationale:* Neuroleptic dysphoria (ND) is a subtle and under-recognized side effect of antipsychotic drugs. It is an all-inclusive descriptive phrase that encompasses a variety of unpleasant subjective changes in arousal, mood, thinking and motivation induced by neuroleptic drugs. Understanding this phenomenon has wide ranging clinical and research implications. *Objective:* The present review examined the themes identified in the original studies from the neuroleptic era in the light of recent findings from neuroimaging research, cumulative experience with second generation antipsychotic drugs, and new concepts such as pleasure responsivity, hedonic regulation and subjective tolerability. *Methods:* Empirical studies on neuroleptic drugs involving clinical populations treated for schizophrenia, Tourette's disorder and stuttering, studies performed on normal healthy volunteers and selected experimental studies in animals, are reviewed. *Results:* Dysphoric responses occur early during treatment and typically manifest as a dislike towards medication (drug aversiveness). Dysphoria persisting over time, may lead to adverse clinical consequences such as treatment non-adherence, substance abuse, poor clinical outcome, increased suicidality and compromised quality of life. Interference with the physiological processes of hedonic capacity by the neuroleptics due to their dopaminergic blocking action in the prefrontal cortex and the shell of nucleus accumbens is the putative mediating mechanism underlying the occurrence of dysphoric responses. Second generation antipsychotic drugs with an atypical receptor blocking profile are less likely to elicit dysphoric responses. *Conclusion:* Viewing neuroleptic dysphoria within a broader spectrum of disorders of subjective tolerability and exploring its neurobiological mechanisms is relevant to addressing the nuances of antipsychotic therapy, and could help unravel the questions surrounding the pathophysiology of depression, substance abuse and other dysphoric clinical states.

Keywords Antipsychotic drugs · Nucleus accumbens · Dopamine · Schizophrenia · Subjective tolerability · Outcomes

This paper is dedicated to the late Theodore ("Ted") Van Putten, (1938–1993), who is fondly remembered as an elegant scholar, a gifted teacher, a pre-eminent schizophrenia researcher, an uncompromising scientist, and a warm and caring doctor. Dr. Van Putten pioneered the study of subjective responses to antipsychotic drugs, and inspired a generation of researchers to explore the phenomenon of neuroleptic dysphoria and elucidate its neurobiological basis.

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Introduction

The success of neuroleptic medications has been punctuated by waves of concerns, about their extrapyramidal side effects (EPS), tardive dyskinesia (TD), neuroleptic malignant syndrome (NMS) and more recently, neuronal apoptosis (Harrison 1999; King and Voruganti 2002). Neuroleptic dysphoria is a less well studied but arguably a more significant adverse effect of the drug therapy from a patients' perspective (Awad 1993). The purpose of this article is to review the literature on neuroleptic dysphoria, and examine its relevance to the modern clinical psychopharmacology.

Nomenclature and historical perspective

The word dysphoria is derived from two Greek syllables (dys=hard/bad, and phoria=to bear). In his *Textbook of Insanity*, C.A. Mercier defined dysphoria as "misery in various degrees", and described it as "the most frequent

and widespread of all disorders of the mind" (Mercier 1914). The term has been widely used in European literature on psychopathology to represent an unpleasant mix of emotions, such as feeling morose, irritable, surly, crabby, mistrustful and hostile (Jaspers 1963; Scharfetter 1980). "Discontent", "grumpy", "nagging" and "annoyed" have been other terms used to describe the feeling (Hinsie and Campbell 1980). It has been also interpreted as dejection, disaffection or abasement (OED 1989). Adoption of the term "dysphoria" into the Anglo-American literature has varied considerably (Fleischhacker 1998). Some equate sadness with dysphoria (as opposed to euphoria), while many consider dysphoria as a global, non-specific, descriptive term that represents a mixture of unpleasant emotions (APA 1984).

Dysphoric feelings, induced by drugs and/or related to illness, are prevalent in a number of neuro-psychiatric disorders, and the term dysphoria has been used as a descriptive prefix in a variety of clinical syndromes such as senile dysphoria (Post 1962), dysphoric mania (Goodwin and Jamison 1990) and late luteal phase dysphoric disorder (LLPDD) (Endicott 2000). Substance abuse is viewed by some as an endogenous dysphoric state, which is relieved by a learned maladaptive pattern of self-medicating behaviour (Khantzian 1985; Dixon et al. 1991). Paroxysmal dysphoric states are also a well recognized manifestation of temporal lobe epilepsy and various personality disorders (Jaspers 1963; Blumer 2000). Unlike these idiopathic clinical disorders, neuroleptic dysphoria is an iatrogenic consequence of antipsychotic drug therapy, which seems to manifest itself as complaints of intolerance, drug aversiveness, drug refusal and non-adherence to treatment. The heuristic value of considering these disparate dysphoric syndromes together and examining their origins may offer insights into their common pathophysiology.

Concept of neuroleptic dysphoria

Unpleasant subjective effects induced by neuroleptics leading to an instant dislike towards these drugs were identified soon after the introduction of chlorpromazine in the 1950s, and these phenomena were described under a variety of descriptive labels (see Table 1). The term "dysphoria" was initially used in the context of studying the effects of neuroleptics (Singh and Smith 1973), and the phrase has since remained as a convenient expression for describing the range of subtle and unpleasant subjective responses related to antipsychotic drug therapy.

Descriptions from earlier reports tended to be broad in their scope, and grouped together as *psychic*, *behavioural* or *mental* side effects together with the sole purpose of distinguishing them from somatic and neurological side effects. Some of the terms (e.g. behavioural toxicity) were over-inclusive; not only did they include side effects, but also the rare paradoxical worsening of psychosis observed during the course of neuroleptic use (e.g. phenothiazine induced decompensation) (Hollister 1957; May 1959; Van Putten et al. 1974; Bowers and Swigar 1988). Other concepts were narrower in their scope, with affective, cognitive, behavioural or attitudinal overtones evident from their descriptions. Terms such as neuroleptic dysphoria, neuroleptic anxiety syndrome and neuroleptic anhedonia carried the connotation of an affective disturbance, while others such as "neuroleptic induced deficit state" suggested that cognitive and motivational difficulties related to antipsychotic drug therapy could also be expressed by patients as dysphoric responses (Knights and Hirsch 1981; King and Henry 1992). There was also a popular notion that neuroleptic dysphoria may be a subjective counterpart of extra-pyramidal side effects such as mild akinesia or subclinical forms of akathisia (Rifkin et al. 1975; Van Putten et al. 1981; Awad and

Table 1 Subtle and under-recognized side effects of conventional antipsychotic drugs

Term and source	Original descriptions
1. Adverse behavioural effects, psychotoxicity, behavioural toxicity, neuroleptic-induced deficit syndrome (NIDS) (Hollister 1957; Van Putten and Marder 1987; Lewander 1994)	Global, unspecified descriptive terms used to encompass the adverse effects of antipsychotic drugs on vigilance, cognitive, conative, affective and motivational faculties of the psyche, distinguishing them from the objective readily recognizable consequences (e.g. motor and autonomic manifestations)
2. Neuroleptic dysphoria (Van Putten 1978; Caine and Polinsky 1979; Singh and Kay 1979; Brunn 1988)	Dysphoria was characterized by a varied mixture of anxiety, agitation, belligerence, depression, accusatoriness, hostility, somatic preoccupation, repetitious importuning, guilt and suicidal ideation; Feeling blah, listless, tired and lacking interest and ambition. Mood change was unrelated to akinesia, drowsiness or cognitive deficits
3. Akinetic depression, subjective extra-pyramidal side effects (Ayd 1958; Klein and Davies 1969; Rifkin et al. 1975; Van Putten 1978; Owens 1996)	Affective manifestation of an extrapyramidal reaction; depression of mild to moderate magnitude characterized by sadness, hopelessness, somatic concern, anxiety, emotional withdrawal, blunted affect and motor retardation; relieved by anticholinergic drugs
4. Neuroleptic separation anxiety syndrome (Mikkelsen et al. 1981; Linet 1985; Russel et al. 1987)	Anxiety and panic symptoms exacerbated by separation from parents; school phobia and avoidance behaviour accompanied by tearfulness; observed in children treated with haloperidol or pimozide
5. Neuroleptic induced psychic indifference (Kalinowski 1958; Healy 1989)	A behavioural syndrome resulting from the effects of antipsychotic drugs on arousal mechanisms, subjectively ego-syntonic or ego-dystonic
6. Dyscognitive syndrome (Heinrich and Tegeler 1983)	A clinical state characterized by apathy, disturbed cognitive functions and associated extra-pyramidal symptoms, induced by neuroleptics

Hogan 1985; Barnes and Braude 1985). The lack of clarity about the concept led to inconsistencies in the use of the term and gave rise to a confusing array of labels. For example, based on the presence or absence of adverse subjective responses, patients were classified as "dysphoric" or "euphoric" (Van Putten 1978), "dysphoric" or "syntonic" (Bartkó et al. 1987; Pi et al. 1990) or "drug resistors" versus "acceptors" (Raskin 1961).

Definition, clinical characteristics and diagnosis

There are three potential sources of subjective distress in psychosis: i) anxiety, fear, depression and dejection related to the positive and negative symptoms (Freedman 1974; Strauss et al. 1989), ii) feelings of discomfort resulting from adverse events such as rigidity, tremor or akathisia (Chapman 1990; Harrow et al. 1991; Halstead et al. 1994), and iii) an uneasy awareness of "lack of pleasure" resulting from the neuroleptic use (Healy 1989; Harrow et al. 1994). It is the latter response that constitutes the concept of dysphoria, which is relatively subtle and solely subjective, making it difficult to define or diagnose with certainty. Hence, the definitions are reviewed at first, followed by a discussion about diagnostic criteria.

In one of the earliest reviews on the subject, DiMascio and Shader (1972) critically examined the scope of the concept, and attempted to arrive at a definition. They concluded that the phrase "behavioural toxicity denoted those pharmacological actions of a drug that produce...*detrimental changes in behaviour and functioning* through alterations in perceptual and cognitive functions, psychomotor performance, motivation, mood, interpersonal relationships, or intra-psychic processes of an individual to the degree that they interfere with or limit the capacity of the individual to function within his setting or constitute a hazard to his physical well-being" (DiMascio and Shader 1972). In subsequent years, patients' global judgements about medications emerged as a practical means of identifying dysphoria. It was noted that "dysphoric responders are those patients who habitually complained about the drug effect; they felt miserable on the drug, and continually pleaded to have the drug stopped or dosage reduced" (Van Putten et al. 1974). Consequently, neuroleptic dysphoria came to be defined, simply, as a "generalized feeling of unwellness that the patient attributes to the neuroleptic" (Weiden et al. 1989). The consensus opinion is that i) neuroleptic dysphoria is an intangible, subjective feeling of dislike towards antipsychotic medication; a clinician may not see any outwardly noticeable signs of distress, and has to rely largely on patients' self reports, ii) the experience is directly attributable to the pharmacological actions of a drug, and may occur even within the therapeutic dose range; and manifest after administering even a single dose of a neuroleptic, iii) it is a global, indivisible experience, not amenable for categorization as a disturbance of mood, cognition or behaviour.

The task of delineating the key elements of the phenomenon has been addressed in a recent neuroimaging study which has attempted to recreate an experimental model of neuroleptic dysphoria. Dysphoric responses were successfully induced among a group of drug-free schizophrenic patients through administering alpha-methyl paratyrosine (AMPT), an agent which blocks catecholamine synthesis and disrupts dopamine's functions temporarily. Serial recordings of subjective mental status over a 48-h experimental period revealed predominant changes in the spheres of vigilance, mood, motivation and cognition (Voruganti et al. 2001). Identifying these themes and variations is not only essential for arriving at a better definition of neuroleptic dysphoria, but also to reliably measure it in the clinical setting.

However, in order to confirm the presence of neuroleptic dysphoria, other concomitant or confounding phenomena need to be ruled out. These include patients' perception of, and reactions to, other side effects such as akathisia and parkinsonian symptoms, and affective disturbances of moderate to severe degree, not infrequent during the course of schizophrenia and antipsychotic drug therapy. The latter include demoralization syndrome, pseudodepression (akinesia mimicking as depression) and postpsychotic depression, which can obfuscate the recognition of neuroleptic dysphoria (McGlashan and Carpenter 1976; Van Putten and May 1978; Siris 2000).

Prevalence and determinants of neuroleptic dysphoria

Dysphoric feelings have been described during neuroleptic therapy of a variety of clinical conditions (schizophrenia and other psychotic spectrum of disorders, Tourette's syndrome, stuttering etc.), and the prevalence rates varied considerably between 5 and 40% (Weiden et al. 1989). The reported variations in incidence and severity were noted to be associated with the following factors.

Medication related factors

Dysphoria was noted to be associated more frequently with the use of high-potency antipsychotic medications (e.g. haloperidol), drugs with predominant D_2 blocking effects, higher dosages, and with other neurological effects such as akinesia and akathisia (Caine and Polinsky 1979).

Illness related issues

The subgroup of nuclear, non-paranoid type of schizophrenic patients, with milder psychopathology scores (at baseline), low urinary homovanillic acid (HVA) levels, and those who did not show therapeutic response in the initial few weeks, were noted to experience dysphoric

responses more frequently. Patients' age and the duration of untreated psychosis did not seem to influence subjective responses (Singh and Smith 1976; Hirsch et al. 1989; Awad 1993; Lysaker et al. 1995).

Personality factors

Personality type (extroversion) and autonomic arousal (elevated pulse rate) during the first 2 weeks of treatment were also noted to be significantly associated with dysphoric responses (Kornetsky and Humphries 1957; Heninger et al. 1965; McDonald 1967).

Environmental factors

Animals' dysphoric responses to neuroleptics (detected by "emotional defecation" rate as an index of heightened arousal) were more evident in novel experimental settings, compared to their behaviour in home cage (Hall 1934; Janke and Debus 1972; Sanberg et al. 1989). The clinical significance of this observation remains unexplored.

Clinical consequences of neuroleptic dysphoria

Dysphoric feelings have been reported to occur within few hours of administering the first dose of antipsychotic medications, and seem to persist over the following weeks and months leading to a number of important clinical consequences (Serafetinides and Clark 1973; Sachdev 1995). The immediate clinical manifestations include complaints of subjective intolerance, reluctance to take antipsychotic drugs or even an outright refusal of treatment (Van Putten 1978). Failure to address these problems may lead to long-term consequences such as non-adherence to treatment, clinical instability characterized by relapses and re-hospitalizations (Blyler and Fenton 1997), suicidal behaviour, co-morbid substance abuse (Awad and Hogan 1985; D'Mello et al. 1995;

Table 2 A summary of the seminal studies on predictive validity of neuroleptic dysphoria

Source[a]	Results and conclusions
1. Singh and Smith (1973)	A multi-purpose study of the dynamics and kinetics of neuroleptic drug (haloperidol) therapy over a 6-month period, involving ten schizophrenic patients. Occurrence of dysphoria was an incidental observation; noted to be associated with less favourable clinical outcome
2. Singh and Smith (1976)	Similar study using both chlorpromazine and haloperidol, involving 18 acute schizophrenic patients; dysphoric response noted in 44%, unrelated to extrapyramidal symptoms (EPS) or the type of drug. Dysphoric response shown to have strong predictive value
3. Van Putten (1978)	A naturalistic study of 42 schizophrenic patients with relapse, treated with chlorpromazine; dysphoria observed in 40% of the sample, linked to medication refusal and poor prognosis
4. Singh and Smith (1976)	Replication of an earlier study involving 58 acute schizophrenic patients, followed up for a year. Dysphoria noted among 52% of the subjects, associated with non-paranoid schizophrenia, high pulse rate and hyper-arousal; associated with poor prognosis
5. Van Putten et al. (1981)	Subjective responses to thiothixene were studied in 63 schizophrenic patients;22% of subjects experienced dysphoric responses and refused treatment. Treatment non-adherence was highlighted as a mediating factor leading to an eventual poor outcome
6. Fink (1982)	A descriptive study of 33 patients with schizophrenia, schizo-affective disorder or affective disorder, treated with various medications; 21% experienced dysphoria, which did not correlate with diagnosis, type of medication, side effects or outcome
7. Ayers et al. (1984)	Subjective responses studied as a part of a controlled clinical trial of drug therapy and social skills training; 70% reported dysphoric responses after 24 h; dysphoria was not related to any of the clinical or treatment variables, not did it have an impact on the outcome at 9 months
8. Awad and Hogan (1985)	55 schizophrenic patients were randomly assigned to chlorpromazine or haloperidol, and subjective responses measured with the drug attitude inventory (DAI); 40–56% were noted to have dysphoria, which was unrelated to the symptom profile or side effects; non-dysphoric responders showed greater improvement at 3 weeks
9. Bartko et al. (1987)	Predictive value of early subjective responses studied in 33 female schizophrenic subjects, treated with a fixed dose (18 mg) of haloperidol; 21% experienced dysphoria, and augured poor prognosis
10. Weiden et al. (1989)	Attempt to characterize neuroleptic dysphoria and determine its predictive validity in 50 patients with various diagnoses, treated with various neuroleptics; 26% reported dysphoric responses; dysphoria correlated with akinesia, lower premorbid functioning, and lower neuroleptic dosing. Neuroleptic dysphoria portrayed as a healthy physiological signalling mechanism against the noxious antipsychotic assault!
11. Pi (1990)	Studied the predictive validity of early subjective responses in 17 schizophrenic patients, in a randomized, double-blind, placebo-controlled trial; 70% of the subjects on thioridazine experienced dysphoria, while none in the placebo group reported dysphoria; early subjective responses had no correlation with outcome at 4 weeks

[a] Listed chronologically

Voruganti et al. 1997; Buckley 1998), compromised quality of life, and increased health care costs (Diamond 1985; Awad et al. 1995; Weiden and Olfson 1995). The emergence of early dysphoric responses may also have a predictive value in determining long term clinical prognosis. Much of the interest in neuroleptic dysphoria in the 1970s was specifically directed at addressing this issue (Galbrecht and Klet 1968; Lindström 1994). The occurrence of dysphoric responses early during neuroleptic therapy was widely believed to augur a poor clinical outcome. A review of literature revealed that eight out of the 11 published studies on the subject reported an association between early dysphoric responses and unfavourable clinical outcome, while two others failed to find such association (Table 2).

From a clinicians' perspective, the association between neuroleptic dysphoria and non-adherence to treatment is a significant clinical matter. Dysphoric responses were noted to contribute to non-adherence with antipsychotic treatment, which in turn leads to an unsatisfactory clinical course and outcome (Van Putten et al. 1981; Rabinowitz et al. 2001; Voruganti et al. 2002).

Measuring neuroleptic dysphoria

Attempts have been made over the years at capturing and quantifying subjective responses to neuroleptic drugs using a number of rating scales (see Table 3). The scales vary in terms of their purpose, length, content, time frame of reference, and mode of administration. The majority are relatively short in length, and are meant to be self administered, which is helpful for sensitively capturing the subjective feelings and responses to drugs. However, differences exist in terms of the content, and time frame. Some are clearly directed at capturing the subjective effects of medications, especially immediately following a single dose administration (e.g. ARCI and POMS), while the others (e.g. DAI, ROMI and PETiT) were designed to capture not only the subjective responses to drugs, but also their long-term consequences (e.g. attitudes toward drug therapy, treatment-adherence and psychosocial functioning). Some are global in their approach (NDS) while others are multidimensional (DAI, SWN); some are generic rating scales (ARCI), while others have been designed for use during antipsychotic drug therapy (SWN); and one (DRI) was made up of selected items from an existing scale (BPRS).

Besides the ones listed here, there have been a number of custom-built visual analogue scales (VAS) and Likert

Table 3 Measuring subjective responses to psychotropic drugs—a summary of selected rating scales

Scale and source	Description	Comments
1. Addiction Research Center Inventory (ARCI) (Haertzen 1965)	77 item self/interviewer administered checklist devised to record subjective responses to a variety of psychotropic drugs; chlorpromazine subscale elicits the subjective effects of neuroleptics	An original subjective responses scale, developed in the context of studying the link between subjective effects and abuse liability of various drugs. Used in drug abuse research; psychometrically sound. Little used in studying antipsychotics
2. Neuroleptic Dysphoria scale (NDS) (Van Putten and May 1978)	4-item clinician-administered questionnaire designed to elicit patient's global subjective responses to antipsychotic drugs	A pioneering attempt to quantify subjective responses; simple, popular, but fails to yield information on the nature of subjective responses. Psychometric properties haven't been established
3. Dysphoric Response Index (DRI) (Singh and Kay 1978)	The sum of six specific items of the BPRS with differential weights attached to them forms the DRI	Shown to be useful as a prognostic indicator; however, a symptom based measure, little used elsewhere
4. Drug Attitude Inventory (DAI) (Awad and Hogan 1985; Awad 1993)	30-item self administered scale aimed at capturing patient's subjective responses as well as attitudes towards drug therapy and other health care services. Available in over 12 languages	First attempt to systematically explore and quantify subjective responses. Easy to use; yields a global score as well as subscale scores; psychometrically sound. Extensively used in drug trials, and other clinical psychopharmacology research
5. Profile of Mood States (POMS) (McNair et al. 1992)	72-item generic, self report checklist; items represent ten categories of emotional states	Widely used for recording the subjective effects of drugs; items limited to various mood states; generic scale
6. Rating of Medication Influences (ROMI) scale (Weiden et al. 1994)	20-item semi-structured scale measures subjective responses and other factors related to treatment-adherence; completed by trained clinician after an interview	Comprehensive in content; developed and tested systematically; primarily developed for monitoring compliance, but not devoted to eliciting subjective responses
7. Subjective Well-being on Neuroleptic medications (SWN) scale (Naber et al. 2002)	20-item self-administered scale, with five sub-scales; yields a total score as well as sub-scale scores. Available in 16 languages	New, focussed, purpose-built and psychometrically sound instrument; easy to use. Widely popular in clinical trials and research studies
8. Personal Evaluation of Transitions in Treatment (PETiT) (Voruganti and Awad 2002)	30-item self-administered scale designed to capture three aspects of antipsychotic therapy–subjective effects, quality of life and treatment-adherence	New, specific, purpose-built and psychometrically sound instrument; easy to use. Being used in a number of clinical trials and other outcome research studies

Table 4 Evidence implicating dopamine in the regulation of pleasure and reward mechanisms

Types of studies	Observations summarized	Selected references
Impaired dopamine function		
1. Hypo-dopaminergic clinical states—Parkinson's disease, deficit states associated with schizophrenia, a sub-category of depressive disorders	Lowered dopamine is linked to the triad of dysphoric mood, tardy thinking and motor slowing, common to all three clinical conditions	(Vogel 1982; Gotham et al. 1986; Swerdlow and Koob 1987; Friedenberg and Cummings 1989; Bermanzohn 1992; Diehl and Gershon 1992)
2. Anti-dopaminergic drug studies		
a. Dopamine depleting agents (AMPT, tetrabenazine and reserpine)	Affective disturbances of variable severity and duration are frequent	(Goodwin et al. 1972; Lang and Marsden 1982; Jankovic 1983; Delgado et al. 1993; Laruelle 1995)
b. Receptor blocking agents (neuroleptics)—use in normal controls, schizophrenia, Tourette's syndrome and stuttering	Dysphoric-depressive responses are known side effects in all populations treated with DA blocking drugs, irrespective of the diagnosis	(DiMascio and Shader 1972; Singh and Smith 1973; Bellmaker and Wald 1977; Van Putten and May 1978; Caine and Polinsky 1979; Anderson et al. 1981; Brunn 1988; Bloch et al. 1997)
3. Animal studies—cerebral lesioning, stimulation, auto-radiography, micro-dialysis and observational studies, using dopamine antagonists (6-OHDA)	Animals exhibit withdrawal and "emotional defecation", often considered as an index of dysphoria	(Russel et al. 1987; Bignami 1991; Emerich and Sanberg 1991; Fibiger 1995)
Elevated dopamine function		
1. Hyper-dopaminergic clinical states—physical and psychiatric diseases—(acute psychosis, mania)	Hyper-vigilance, over-activity, heightened mood and perception are common features	(Gerner et al. 1976; Silverstone 1984; Gessa et al. 1995)
2. Dopamine agonist studies		
a. Clinical studies—L-dopa, apomorphine, piribedil and bromocriptine	Psychosis and mood alterations are frequent side effects	(Murphy 1971; Post et al. 1978; Cantello et al. 1986)
b. Substance abuse literature—amphetamine, cocaine and PCP users	Dose-activity relationship characterized by increased arousal, over-activity and enhanced mood, to be followed by disorganization, and onset of psychosis, corresponding to the increase in dopamine levels demonstrated in both human and animal experiments	(Fibiger 1995; Wise 1996; Koob 1997; Koepp and Grasby 1998)
c. Drug self-administration studies (in human volunteers)	–	(Schuster and Thompson 1969; Piazza et al. 1989)
3. Animal studies—intracranial self stimulation (ICSS) and drug self-administration paradigms	–	(Leith and Barrett 1976; Roberts et al. 1989; Markou and Koob 1991)

scales, used in a number of studies based on their face validity. After 25 years of research in the area, the most popular technique for eliciting subjective responses to a drug seems to be a single, direct, closed-ended question with a choice of two answers: "I like it", or "I don't like it"! Of course, such an assessment assumes that dysphoria is a static response that is not altered by changes in experience.

What causes neuroleptic dysphoria?

The label neuroleptic dysphoria carries a connotation that the adverse experience is readily attributable to the use of neuroleptic drugs, though such a causal association is somewhat presumptive. Theoretically there have been three possible mechanisms suggested to explain the dynamics underlying neuroleptic dysphoria. The *medication-centred model* implicates drugs as exclusively responsible for ND. Evidence to support such an assertion came from studies using a variety of techniques including experimental self report studies, clinical studies, epidemiological data, and experimental work in animals (see Table 4). Some researchers also observed that the incidence of affective disturbances in schizophrenia seemed to have increased dramatically after the introduction of modern antipsychotic drugs (Hollister 1957; Van Putten 1978; Siris 2000). This *illness model* proposes that dysphoria is an integral part of the underlying disease process, and drug therapy is merely instrumental in bringing out the latent affective disturbances. There is an emerging notion in recent years that the biological underpinnings of schizophrenia, especially the involvement of dopaminergic system, leads to "hedonic homeostatic dysregulation" which makes individuals prone for dysphoria, and substance abuse in later years (Koob and LeMoal 1997; Rosenthal 1998; Chambers et al. 2001). Reports on the occurrence of dysphoria in non-psychotic disorders (tic disorders and stuttering) are a reminder that the phenomenon is not illness-specific. The *interactional model* implies that both individual's vulnerability and neuroleptic drugs are essential for ND to manifest (Piazza

et al. 1989; Piazza and Le Moal 1996). Though the role of antipsychotic drugs in causing dysphoria has been adequately explored, it is notable that only a proportion of patients treated with antipsychotic drugs experience dysphoric feelings, suggesting that dopaminergic blockade alone may not always be the sole cause of dysphoria. The contribution of an individual's neurobiological make up towards the development of dysphoria is considered equally critical (Voruganti et al. 2001).

Psychodynamic aspects of dysphoria

Sarwer-Foner described quite eloquently that the role of patients' perceptions and attitudes towards drugs, as crucial in the overall therapeutic process (Sarwer-Foner 1963). In his proposed psychodynamic explanation of the mechanism of action of neuroleptic drugs, he stated that "the therapeutic effect depends on the manner in which the patient integrates the pharmacological profile of the drug concerned into his total situation". He contended that "the typical pharmacological effect chemically removes or interferes with activities used by the patient as major defences against unconscious underlying conflicts". Patients who interpreted these actions as "good" seemed to fare well, and those who perceived the drugs as "bad" for them showed unfavourable results or even paradoxical drug reactions. These sentiments were echoed by others as well, and the general consensus was that, among the dysphoric responders, neuroleptic medication interferes with a "psychotic equilibrium", however maladaptive it could be (Nevins 1977). Other researchers interpreted the phenomena of drug refusal and subsequent non-adherence with maintenance neuroleptic treatment as learned behaviours, closely linked to the initial subjective experience of various side effects. The negative impact of these experiences on future treatment adherence was explained in terms of interoceptive conditioning (Barofsky 1976). It was interpreted that the ingestion of antipsychotic medication and the occurrence of dysphoric response as a paired event would lead to a subsequent conditioned response of drug refusal and treatment non-adherence (Van Putten et al. 1981).

Pathophysiology of neuroleptic dysphoria

In their original review, DiMascio and Shader (1972) concluded that behavioural toxicity was of idiopathic origin, and predicted that "the scope of what is included under this heading will progressively diminish as we are able to specify more and more the biochemical or neurophysiological determinants of a given behaviour" (DiMascio and Shader 1972). In the ensuing 25 years, basic sciences research has shed much light on the neurobiological mechanisms involved in experiencing both pleasurable and dysphoric effects of various psychotropic drugs. With the recent developments in neuroimaging and molecular genetics, it has become possible now to discuss the putative mediating mechanisms of neuroleptic dysphoria in terms of neuro-anatomical, neuro-chemical and molecular mechanisms.

Neuro-anatomical aspects

Currently, it is believed that there is a common neurobiological substrate ("brain reward system") for the mediation of subjective responses to a number of psychotropic drugs, illicit as well as prescribed. Alterations involving these pathways lead to drug addiction on the one hand, or drug aversion on the other. Earliest studies involving intracranial self-stimulation in animals identified medial forebrain bundle connecting the ventral tegmental area and the basal forebrain as crucial in the mediation of positive reinforcement effects of misused drugs. It is now clearly established that the mesocorticolimbic dopamine system forms the neural substrate for pleasure responsivity and reward systems (Fibiger and Phillips 1986; Wise 1988; Self and Nestler 1995; Koob 1997). The key components of this circuitry are ventral tegmental area (site of dopaminergic cell bodies), basal forebrain (nucleus accumbens (NAc), olfactory tubercle, frontal cortex and amygdala), and the median forebrain bundle connecting these two structures (Volkow and Fowler 2000). As a prominent part of the ventral striatum, and as the main target of the mesotelencephalic dopamine system, nucleus accumbens has been implicated in the control of reward and motivational aspects of behaviour (Heimer et al. 1997). Nucleus accumbens septi is a vaguely defined anatomical area of the basal forebrain, situated between the subcortical striatal system and the limbic system. Two parts of the accumbens are now identified—a central striatal "core", and a limbic "shell". The shell is a part of the extended amygdala, rich in dopaminergic neurons that are implicated in mediating substance abuse and possibly psychotic states. The functional significance of this neuro-anatomical differentiation is supported by recent observations that neuroleptics exert their actions on both the core and the shell, while atypical antipsychotic drugs act predominantly on the core of the nucleus accumbens and medial pre-frontal cortex, as demonstrated by the *neurotensin* and *Fos* immunoreactivity studies (Taber et al. 1995; Kuroki et al. 1999).

Neurochemical aspects

It has been clearly established in recent years that dopamine plays a crucial role in the regulation of pleasurable feelings; increased dopamine activity (in the mesolombic system) is associated with the experience of pleasure, while decreased dopaminergic activity leads to unpleasant or dysphoric feelings (Fibiger 1995; Self and Nestler 1995; Wise 1996; Koob and LeMoal 1997). Evidence supporting this view is derived from a number of clinical and animal studies, which are summarized in

Table 4. Despite its compelling nature, much of the past evidence has been circumstantial in nature; and no direct evidence was available until recently to substantiate dopamine's mediating role in the induction of dysphoric responses.

Recent neuroimaging studies, especially in the field of receptor quantification, have facilitated direct visualization of synaptic dynamics and correlate them with clinical events (Volkow et al. 1999). These reports found an association between cortical D_2 receptor binding potentials (BP), depressive symptoms and dysphoric responses (Hietala et al. 1999; de Hann et al. 2000; Fujita et al. 2000). Recently, in a focussed investigation aimed at addressing the relationship between dopamine and dysphoria, it was shown that disrupting catecholaminergic function through administering alphamethyl paratyrosine (AMPT) leads to a characteristic dysphoric syndrome (Voruganti et al. 2001). The study has also found an inverse relationship between prevailing striatal dopaminergic activity and the severity of dysphoric responses, i.e. the subgroup of subjects with lower dopaminergic activity prior to the AMPT administration reported significantly higher dysphoric feelings, while those with greater elevations in dopamine experienced minimal dysphoria. The cumulative evidence, thus, confirms that dopamine plays a critical role in the regulation of affect and hedonic capacity, and neuroleptic induced dopaminergic blockade impairs this physiological function and induces dysphoric feelings.

The purported role of dopamine is becoming increasingly complex with the availability of new data on the dynamic processes involving receptor blockade (Kapur and Seeman 2001). Also, there is growing evidence that other dopamine receptors, especially D_4 may have a role in the mediation of pleasure responses and sensation seeking behaviour (Ebstein et al. 1996). Also, there is a need to consider the modulating effects of serotonin, acetylcholine and noradrenaline on the dopaminergic system (Kahn and Davidson 1993; Westerink et al. 2001). The second generation antipsychotic drugs with atypical receptor blocking profiles have been found to carry a lower risk of inducing dysphoric responses, and preliminary clinical studies confirmed that lower rates of dysphoria improved treatment adherence and psychosocial outcomes (Rabinowitz et al. 2001; Voruganti et al. 2002).

Pharmacogenetic considerations

The evidence so far indicates that the occurrence of dysphoria is not merely a function of the receptor blocking profile of antipsychotic drugs, but is a result of an interaction between dopaminergic blockade and the innate vulnerability of some individuals (Voruganti et al. 2001). Such vulnerability may operate through inter- and intra-individual variations in dopaminergic function or modulation of dopaminergic activity by serotonin, acetylcholine and other neurotransmitters. Future research should focus not only on the receptor profiles of antipsychotic drugs, but also on studying the idiosyncratic nature of the dopaminergic system among individuals that are predisposed to develop dysphoria.

The role of genetic factors in general, and variations involving dopamine and serotonin receptor and transporter genes in particular, in determining the nature and magnitude of subjective responses to drugs, has become an area of intense investigation in recent years. It is realized that the sequence diversity of these genes could dictate the neurochemical individuality of humans and their predisposition to hedonic dysregulation (Cravchik and Goldman 2000). A series of recent genetic investigations seem to indicate that common polymorphisms involving the dopamine receptor D_4 (DRD_4), the dopamine transporter (DAT), the serotonin transporter promoter region (5HTTLPR), and the catechol-o-methyltransferase (COMT) enzyme may account for the individual differences in personality traits through contributing to brain dopaminergic tone. Genes modulating dopamine levels or receptor response, thus, could contribute to higher level of expressions of these molecular events underlying hedonic dysregulation (Ebstein et al. 1996). Gene knock-out mice deficient in D_3 and D_4 receptors displayed reduced anxiety responses and locomotor supersensitivity to ethanol, cocaine and methamphetamine, providing indirect evidence to the notion of genetic determinants of subjective responses to drugs (Rubenstein et al. 1997; Steiner et al. 1997).

Emerging science of subjective tolerability

Neuroleptics conspicuously lack abuse potential; and many patients, indeed, love to hate them. The same clinical population, on the other hand, is known to have an increased susceptibility to substance abuse (Regier et al. 1990). The common underlying theme is the study of subjective responses to administered drugs, their reinforcing effect on motivational behaviour, and the resultant behavioural/clinical consequences. Neuroleptics, by virtue of their dopaminergic blocking effect in nucleus accumbens induce dysphoric responses, which lead to negative reinforcement and therapeutic non-compliance in the clinical context. Drugs with abuse liability, on the other hand, produce euphoric responses (subjective "high") through enhancing dopaminergic transmission in the same mesolimbic circuits, perpetuate a cycle of positive reinforcement and eventually result in substance abuse (Volkow 2001). The shared characteristics of subjectivity, reinforcing mechanisms and common neurobiological substrates makes it logical to designate the spectrum of these drug induced dysphoric and euphoric states as "disorders of subjective tolerability" (Voruganti et al. 1997).

Study of the cascade of events at cellular and molecular level, especially the post-receptor signal transduction will be critical towards understanding the perpetuation of dysphoric responses to neuroleptics and

their long term consequences. According to the paradigm of "initiation and adaptation" (Hyman and Nestler 1996), the neuroleptic drug induced dopamine blockade is considered as an initiating event; and the continued administration of drugs leads to an adaptive response consisting of both qualitative (structural and functional changes involving remodelling of synapses) and quantitative changes (e.g. up-or down-regulation of receptors) in the nervous system. A study of these adaptive changes will provide better understanding as to how the positive or negative subjective responses to an initial dose of a drug ultimately determine the phenomenon of subjective tolerability in longer term.

Other implications

Subjective tolerability is critical in ensuring treatment adherence, and eventually determines the success of antipsychotic therapy of schizophrenia (Blyler and Fenton 1997). In the absence of credible alternatives to dopaminergic blocking drugs, clinicians and researchers were resigned to the idea that neuroleptic dysphoria is an inevitable consequence of drug therapy, and there is little point in complaining about it! (Van Putten 1978; Hollister 1992). However, the arrival of a new generation of atypical antipsychotic drugs with improved subjective tolerability has reversed this trend, and created a renewed sense of hope and optimism (Voruganti et al. 2000; Karow and Naber 2002). Yet, the phenomenon of neuroleptic dysphoria has not disappeared altogether. Dysphoric responses have been noted, albeit much less frequently, with the novel antipsychotic drugs as well. In addition, a sizeable minority of schizophrenic patients continues to require maintenance treatment with conventional neuroleptic drugs. Hence, the study of neuroleptic dysphoria not only has a heuristic value but also has clear implications for clinical practice and new drug development.

Conclusions

Neuroleptic dysphoria has been a clinically significant but inadequately understood phenomenon, a phantom of the neuroleptic era indeed. This article reviewed the original studies on neuroleptic dysphoria, and explored their significance in the light of recent observations from neuroimaging studies and basic science research that explored the relationship between drugs, dopamine and dysphoria. There is an emerging picture that the scope of dysphoria research is not confined to antipsychotic drugs or dopaminergic dysfunction alone. Dysphoria extends to a variety of clinical syndromes characterized by subtle alterations in mood, or more precisely, hedonic dysregulation. The study of neuroleptic dysphoria and actions of antipsychotic drugs, thus, provide an opportunity to unravel the complexities surrounding the pathophysiology of psychosis and its common co-morbid states such as depression and substance abuse. Also, continuing research in this area will have direct implications for the development of newer antipsychotic drugs and enhancing the quality of life of individuals who rely on long-term antipsychotic drug therapy for schizophrenia.

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