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Neuroleptic dysphoria: revisiting the concept 50 years later

Awad AG, Voruganti LNP. Neuroleptic dysphoria: revisiting the concept 50 years later.

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Objective: To review the concept of neuroleptic dysphoria, its historical development and the current state of the art.

and also draws on our extensive clinical and research experiences. **Results:** Although the construct of neuroleptic dysphoria was recognized shortly following the introduction of the first antipsychotic, chlorpromazine, it took several years for the concept to receive adequate research and clinical attention. Without having direct evidence to link neuroleptic dysphoria to dopamine, it was generally understood that dopamine played a significant role in its genesis. In recent neuroimaging studies and dopamine depletion strategies, the role of dopamine in

Method: This paper is based on extensive but selective literature review

the genesis of neuroleptic dysphoria has been directly confirmed.

Conclusion: Neuroleptic dysphoria is a valid construct, which has significant implications for treatment and outcome. It is now clear that it relates to dopamine activities in the nigrostriatal complex. Recent research has also raised the issue of whether neuroleptic dysphoria is a variant of extrapyramidal symptoms. Meanwhile, the role of dopamine in both the genesis of neuroleptic dysphoria and addictive behaviour has raised the issue of both conditions being different facets of the schizophrenic disease process. The recent interface of addiction and psychiatry research may have opened a new science: the science of subjective tolerability disorders.

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Key words: schizophrenia; antipsychotics; neuroleptic dysphoria; dopamine; subjective tolerability

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Introduction

Following the introduction of the first antipsychotic, chlorpromazine, patients complained of altered and unpleasant subjective states that contributed to their dislike or at times, aversion to medications (1-4). Although this phenomenon received different labels in the early literature, it did not receive serious research interests until the early 1970s. The recognition, then, that neuroleptic dysphoria and negative subjective responses to antipsychotic medications can play a significant role in medication non-adherence behaviour (5–7) has brought focused research attention in such phenomena, as reflected by the increased number of publications and the development of a number of reliable scales for the measurement of subjective responses to medications. The majority of the studies was clinical in nature and contributed to better understanding of the concept and its impact

on clinical outcomes. Based on extensive preclinical basic research, from the early 1960s and the clinical observation that dysphoric responses has often been encountered with conventional antipsychotic medications, all of them are potent dopamine D₂ antagonists; a role of dopamine has always been implicated in the genesis of these dysphoric responses (3, 4, 8, 9). Yet, there was not much that clinicians could do differently, at that time, as all antipsychotic medications available then have been potent dopamine antagonists. Similarly, there was no reliable technology to directly explore dopamine activity in the brain. In essence, all that could be done in terms of researching neuroleptic dysphoria has already been done and the field appeared to be on the verge of stagnation. Fortunately, the introduction of the new antipsychotics in the early 1990s with their different mode of action has opened an era of optimism and lead to increased research interests

into whether the new antipsychotics can provide better subjective tolerability (10, 11). Indeed, by the early 1990s, outcomes such as subjective tolerability and quality of life have become recognized as an important outcome to medication therapy (12, 13). At the same time, the introduction of neuroimaging technology has provided the ultimate opportunity to establish a direct link between brain dopamine activities and the development of dysphoric responses. This new understanding not only clarified the genesis of the construct of neuroleptic-induced dysphoria and contributed to better delineation of the phenomena and its relationship to other side-effects but also neuroimaging studies have opened new vistas such as exploring the role of dopamine in the genesis of other conditions such as comorbid drug abuse. which is a frequent concurrent phenomenon in schizophrenia (4, 14).

Aims of the study

In this review, we will attempt to document in detail the historical development of the construct of neuroleptic dysphoria, the reasons for the slow recognition of the concept, its measurement as well as the evolvement of its clinical and research implications.

Material and methods

This review is based on Pre-Medline and Medline database searches as well as the author's database using the following keywords: neuroleptic dysphoria, antipsychotics, schizophrenia, subjective response, subjective tolerability, dopamine and comorbid addictions. As the literature is extensive and much of it is in the form of confirmatory studies, we cited only the key studies that we felt could add new information.

Results

The concept of neuroleptic dysphoria-historical notes

Although the phenomenon of neuroleptic-induced dysphoria has been recognized early, following the introduction of chlorpromazine, it was invariably labelled in the early literature as 'akinetic depression' (15), 'behavioural toxicity' (16, 17) or 'neuroleptic-induced psychic indifference' (18, 19). In 1976, Sing and Smith (2) coined the term 'neuroleptic-induced dysphoria', which is the term most commonly used since then. Other terms have been later proposed such as 'dyscognitive syndrome' (20), 'neuroleptic-induced deficit syndrome' (21),

'neuroleptic-induced anhedonia' (9) and 'negative subjective responses' (7); however, the term 'neuroleptic dysphoria' has continued to be the most popular terminology used in the literature. The term 'neuroleptic dysphoria' unfortunately, is not completely accurate, as it brings the notion of affective changes as the principal component of this construct and frequently becomes confused with the affective state of 'dysphoria' as described in the DSM. As we now know, based on recent research, neuroleptic-induced dysphoria, in addition to the wide-range of affective subjective changes such as dysphoria, anxiety, anger, hostility, depression and dejection, also includes several other cognitive and motor symptoms (22, 23).

Prevalence of neuroleptic-induced dysphoria

Dysphoric responses have been described with virtually all the conventional antipsychotics regardless of the dose and type of medication. Although most of the research has been conducted in patients suffering from schizophrenia, dysphoric responses have been reported in other conditions treated with antipsychotic medications such as Tourette's syndrome or other psychotic spectrum disorders. There is no clear estimate of the incidence, although the prevalence has been estimated to range between 10 and 60% in those patients receiving conventional antipsychotic medications (4). One of the questions that puzzled clinicians and researchers has been the marked variability of the incidence of dysphoric responses and why not all patients with similar diagnosis and receiving similar antipsychotic medications experience such phenomena.

Factors that slowed research in neuroleptic dysphoria

Although the phenomenon of neuroleptic dysphoria has been recognized as early as the 1950s, it took several years for research interests to develop. Several factors, in the early years, may have impeded research interests.

The subjective nature of the phenomena and the reliability of patients self-reports. As schizophrenic patients frequently experience cognitive deficits, disturbed thinking and communication, their reports about their feelings, values and attitudes are often uncritically dismissed as unreliable. Clinicians have traditionally been suspicious of subjective assessment by patients of treatment outcomes. There is, therefore, a paradox in clinical management as clinicians able to base their diagnostic formulations on patients' unobservable self-reports about their unique and personal

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experiences, such as hallucinations and delusions, yet question the reliability of the same patients selfreports about their feelings on medications. This paradox represents the ongoing challenge of how to reconcile subjectivity with the quest for objectivity (24, 25). Several studies have already demonstrated the reliability and consistency of patients self-reports (24, 26, 27). In an early study, we demonstrated that the reliability co-efficient of such self-reports, measured weekly, over a 4-week period, were positive and statistically significant (R = 0.80 - 0.87, P > 0.0001) (24). Furthermore, exploring the reliability of patients self-reports about their assessment of quality of life, which is another subjective construct, we reported significant concordance between patients' subjective selfreports and objective measures conducted by clinicians (24). Repeated measures ANOVA failed to detect any group-by-week interaction effects for the severity of symptoms, side-effects, neurocognitive deficits, antipsychotic doses or attitudes towards medication (24). The lack of such interactions indicates that subjective self-reported scores remained consistent for all subgroups of patients, over time. A recent study reported similar conclusions (28). Significant associations were found between self-reported and objective measures of positive, negative and depressive symptoms, independent of insight level. Obviously, one has to make an allowance that a minority of schizophrenic patients who are suffering from severe psychotic disorganization or marked cognitive impairment and who might also be severely compromised in insight and judgment may not be able to provide reliable self-reports. In other words, the majority of schizophrenic patients, even though symptomatic but stable can provide consistent and reliable self-reports about their inner feelings and level of satisfaction.

The absence of reliable scales for measurement of subjective responses to medications. The lack of reliable and validated scales for measurement of subjective responses have limited research in the early years and may have contributed to the erroneous perception that research in such areas represents 'soft-science'. Fortunately, over the past 25 years, several new scales have been introduced and five of them continue to be in common use:

i) Drug Attitude Inventory (DAI): A 30-item self-administered scale aimed at capturing patients' subjective responses as well as attitudes towards drug therapy (3, 6, 26). A shorter version of 10 items exist (DAI-10), which is focused on positive and negative

subjective states in response to medications and has been proved to be predictive of compliance behaviour. The DAI was the first to attempt to systematically explore and quantify subjective responses. The scale is easy to use and has a global score as well as a subscale score. The scale is psychometrically validated and extensively used in drug trials and other clinical psychopharmacology research. The scale has been translated into several languages.

- ii) *Profile of Mood States*: A 72-item generic selfreport checklist with items representing 10 categories of emotional states (29). The scale is generic and widely used for recording the subjective effects of drugs. Items are limited to various mood states.
- iii) Rating of Medication Influences: This is a 20item semi-structured scale, which measures subjective responses and other factors related to treatment adherence, completed by trained clinicians after an interview (30). The scale is comprehensive in content, developed and systematically tested and primarily introduced for monitoring compliance.
- iv) Subjective Well-being on Neuroleptic Medications: A 20-item self-administered scale with five subscales, which yields a total score as well as subscale scores (31). The scale is purpose built, psychometrically sound, is easy and often used in clinical trials.
- v) Personal Evaluation of Transitions in Treatment: A 30-item self-administered scale designed to capture three aspects of antipsychotic therapy: subjective effects, quality of life and treatment adherence (13). The scale is specific, purpose built and psychometrically validated. The scale has been in use in clinical trials and other outcome research studies.

Neuroleptic dysphoria – clinical studies

A number of early studies, although they were small, mostly uncontrolled and generally descriptive in nature have provided the foundation for subsequent research. In 1973, Singh and Smith (32) reported about the occurrence of dysphoria in the course of their 6-month study of the dynamics and kinetics of haloperidol therapy, in schizophrenic patients. This was probably the first study to document the association of dysphoric responses to medications with less favourable clinical outcome. In 1976, the same authors in a study of acute schizophrenic patients reported that 44% of their patients receiving either chlorpromazine or halo-

peridol had experienced dysphoric responses regardless of the type of medication or extrapyramidal symptoms (2). This study, once more, confirmed the predictive value of dysphoric responses. A similar study by Van Putten and May (33) in 1978, reported that 40% of their sample of relapsed schizophrenic patients treated with chlorpromazine had experienced dysphoria and noted that the occurrence of dysphoria was related to refusal of medications and augured poor outcome. A few subsequent papers, by Van Putten et al. (34-36), from the same group, over the period of 1978–81, has expanded and confirmed earlier reports about the association of neuroleptic dysphoria with medication non-compliance and poor outcomes regardless of the type of antipsychotic. In a subsequent series of papers by Awad et al. (7, 37, 38), negative subjective responses to antipsychotic medications as measured by the DAI, was associated with poor compliance behaviour and eventual poor outcome. Similarly, such dysphoric responses were demonstrated to negatively impact on quality of life, satisfaction with medications and possibly contribute to suicidal behaviour (7, 39–41). Voruganti et al. (42), in another study, demonstrated the association of comorbid drug abuse with dysphoric responses to antipsychotic medications, proposing that neuroleptic dysphoria may be the missing link between schizophrenia and substance abuse (odds ratio 4.08, $\chi^2 = 21.8$, P < 0.0001). The predictive value of early subjective responses in determining treatment outcome has been proposed and confirmed in several reports (26, 31, 33, 37).

Examining the intercorrelations between subjective tolerability as measured by the DAI and clinical indices in a cohort of stable schizophrenic patients attending a clinic (24, 40, 43), significant negative correlations were observed between positive symptoms subscale, general psychopathology subscale and the total score on the Positive and Negative Symptoms scale (PANSS). More significant negative correlations were demonstrated between the occurrence of neuroleptic dysphoria and the PANSS depression and insight items score. Akathisia, as measured by the Hillside Akathisia Scale was also negatively correlated with subjective tolerability to medications but no such correlation was associated with abnormal movements or to the type or dose of antipsychotic medications. In another study of quality of life of medicated stable schizophrenic out-patients, subjective tolerability was negatively correlated with quality of life

A large number of subsequent studies have corroborated and expanded on the early data

linking neuroleptic dysphoria to negative compliance behaviour and poor outcomes (45–48). However, a minority of studies, although having confirmed the high incidence of neuroleptic dysphoria during the course of antipsychotic drug therapy, has failed to establish any link with outcomes (49, 50). It is possible that differences in patient samples as well as design and methodology may have contributed to such negative data. In essence, then, the major bulk of data from clinical studies seems to implicate neuroleptic dysphoria in compliance behaviour and eventual overall outcome.

Neuroleptic dysphoria – recent research

By the early 1990s, all that could be done, in researching neuroleptic dysphoria, within the available methodology, had already been done. New reliable scales have been developed and are in common use. Several clinical studies have clearly demonstrated the negative impact of neuroleptic dysphoria in terms of overall outcome, quality of life and the functional state of schizophrenic patients on medications. The construct has become increasingly recognized by clinicians and, the patients' point of view about their feelings on medications has been increasingly taken seriously by their clinicians. Yet, clarifying the neurobiological basis of neuroleptic dysphoria has been limited by the unavailability of reliable methodology to visualize and quantify dopamine receptor activities in the brain. Fortunately, two major developments in the 1990s activated the research field, once more: the introduction of new generation of antipsychotics with different mechanisms of action and the application of neuroimaging techniques and reliable methodology to directly examine dopamine activity in the nigrostriatal complex.

The introduction of second-generation antipsychotics

The accelerated drug development over the last two decades of the last century has led to the introduction of a series of new medications, which possess a different mode of action than the old first-generation antipsychotics (51). Although new and old antipsychotics have been equivalent, overall, in terms of efficacy, the second-generation antipsychotics proved to be better tolerated, as a result of their favourable side-effects profile (52). Overall they have much less impact on extrapyramidal symptoms, even though they may have brought a range of new side-effects such as metabolic and cardiovascular side-effects. Few clinical studies have demonstrated much less

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neuroleptic dysphoria with the use of secondgeneration antipsychotics (53–56). Although most of the studies have, so far, been uncontrolled, cross-sectional or long-term naturalistic switch studies. A recent review reported a consistent trend towards better subjective tolerability on the new antipsychotics (11). As second-generation antipsychotics are different in their mode of action, a revival of interest in exploring the role of dopamine in the genesis of neuroleptic dysphoria ensued. The availability of these new antipsychotics has presented an opportunity to use them as pharmacological probes for studying the incidence of dysphoria, compared with the old medications and examine the relationship of dysphoria to sideeffects. A detailed review of the impact of new antipsychotics on neuroleptic dysphoria and subjective responses appears in the two contributions by Naber et al. and Marder in this issue of the supplement (57, 58).

Recent neuroimaging studies

The recent availability of reliable neuroimaging techniques to visualize and quantify activities of the dopamine receptor in the nigrostriatal complex (59) has provided the ultimate opportunity to define the role of dopamine in the development of dysphoria and has also allowed better understanding of the individual differences among patients in developing dysphoria. Neuroimaging research of neuroleptic dysphoria has followed two lines of experimental approaches: manipulation of dopamine in the nigrostriatal area employing a depletion strategy with chemicals such as para-aminotyrosene (AMPT) (22, 60). The other approach has been the study of dopamine receptor occupancy under various treatments with the new and old antipsychotics (61, 62). A recent study by Voruganti et al. (22), has successfully managed to experimentally induce dysphoria in medication-free schizophrenic patients by manipulating dopamine activities in the striatal-accumbens complex, thereby directly linking dysphoria to dopamine binding ratios. The results also demonstrated the individual variability of dopamine activities in the nigrostriatal complex, which, for the first time, has clarified why not every patient on antipsychotic medications develops dysphoria. It is clear that only those patients with low basal dopamine activities in the nucleus accumbens are the most vulnerable for development of dysphoria when given potent dopamine D₂ antagonists. The AMPT study has also demonstrated that depletion of dopamine brings about a cascade of symptoms that include significant affective, cognitive, psychological and motor effects (63). It is interesting that the earliest of these effects have been demonstrated to be the subjective experience of neuroleptic dysphoria that occurs after only few hours. Confirmation of the results of this study has recently been reported by Verhoeff et al. (60), using a similar AMPT-induced dopamine depletion strategy. More detailed information about these findings is presented by Voruganti and Awad in this supplement (23).

The other line of experimentation has been the use of PET studies to measure relative occupancy of the dopamine receptor in the nigrostriatal area. The lead work in this area has been presented by de Haan et al. (61, 62). Data from a series of studies, in schizophrenic patients treated with olanzapine or risperidone, has found a significant correlation between dopamine D_2 occupancy and dysphoric responses.

Discussion

The final elaboration of the role of dopamine in the genesis of neuroleptic dysphoria by itself represents a remarkable chapter of dogged and persistent research interests that expanded over 50 years, since neuroleptic dysphoria was first recognized in the 1950s. The recent new imaging studies have confirmed in humans what preclinical studies in animals had proposed several decades ago, in terms of the significant role of dopamine in pleasure, reward and reinforcement behaviour (see the contribution by Bressan et al. in this issue of the supplement) (64). The individual variability in the incidence of neuroleptic-induced dysphoria is now better understood in terms of the dynamic interactions between the state of the dopamine receptor and the pharmacological properties of the medications. This new understanding has significant clinical implications in the management of schizophrenia. The negative impact of neuroleptic dysphoria on compliance behaviour has been adequately documented, leading to relapse and frequent hospitalizations. Similarly, dysphoric responses have been shown to contribute to compromised quality of life and comorbid substance abuse. Although the phenomenon of neuroleptic dysphoria has been described more frequently with potent dopamine D₂ first-generation antipsychotics, it is still relevant with second-generation antipsychotics, albeit with less frequency (53, 54). The new knowledge about the genesis of neuroleptic dysphoria and its close relationship to dopamine receptor status can prove helpful in the development of better tolerated new antipsychotics. Meanwhile, the new research insights in the role of dopamine in the nigrostriatal complex has opened a new vista of research in exploring the role of dopamine in concurrent addictions, which is a common comorbidity in schizophrenia, particularly as both conditions share a common neurobiological substrate (see the contribution of van Nimwegen et al. in this supplement) (65). Some of the new findings from addiction research, coupled with the new insights about neuroleptic dysphoria from recent neuroimaging studies has raised the possibility of whether comorbid drug abuse in schizophrenia may also be another facet of the illness itself over and above the notion of selfmedication (14). Altogether, the converging of research coming from the addiction field as well as the psychopharmacology of antipsychotic medications may have ushered in a new science about 'disorders of subjective tolerability' (14).

In conclusion, the phenomenon of neurolepticinduced dysphoria and its clinical implications has been extensively documented over the past 50 years. Although dopamine activity in the nigrostriatal complex has been suspected to be the culprit, for years, only recently its role in the genesis of this phenomenon has been confirmed in a series of neuroimaging studies. The question of whether neuroleptic dysphoria is a variant of extrapyramidal symptoms has been raised by recent studies but continues to be an open question. Similarly, based on recent research, the frequent association of schizophrenia, neuroleptic dysphoria and comorbid substance abuse has raised the question of whether neuroleptic dysphoria and substance abuse represent different facets of the disease process itself, as dopamine is involved in both conditions and both share common neural circuits. Such recent interface of addiction and psychiatric illness may have opened a new science: the science of subjective tolerability.

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Declaration of interest

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