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Provocative tests with psychostimulant drugs in schizophrenia

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Abstract. The psychotogenic effects of psychostimulant drugs have provided a major line of evidence in support of the DA hypothesis of schizophrenia. To evaluate the effects of psychostimulant (PS) drugs in schizophrenia and the clinical variables which may influence their expression, we reviewed 36 studies of PS drugs in patients with schizophrenia. Approximately 40% evidence a psychotogenic response to PS administration in doses that are subpsychotogenic in normals. Specific clinical variables appear to modify this response, including diagnosis, degree and type of psychopathology, stage of illness and pharmacologic status at the time of testing. Non-amphetamine-like PS drugs, e.g., methylphenidate, appear to have greater psychotogenic potency than amphetamine-like PS drugs. These results suggest the presence of a subgroup of schizophrenic patients who exhibit psychotic symptom activation with PS in a state dependent or independent fashion. This biologic phenomenon may be clinically exploitable and should be investigated further.

Key words: Psychostimulant drugs – Schizophrenia – Methylphenidate – Amphetamine – Provocative test – Behavioral effects

Psychostimulants (PS) are drugs that stimulate the central nervous system (CNS) and sympathetic nervous system through their agonistic effects on catecholamine neurotransmission (Scheel-Krüger 1971; Ferris et al. 1972; Groves and Rebec 1976; Moore 1978). These drugs act predominantly by releasing biogenic amines from their storage sites in presynaptic nerve terminals and blocking their reuptake (Scheel-Krüger 1971; Ferris et al. 1972; Groves and Rebec 1976; Moore 1978), though some agents, e.g., ephedrine, have direct receptor effects as well (Weiner 1980). Acute administration of PS drugs produces psychomotor activation, subjective euphoria, talkativeness, insomnia and anorexia, though paradoxical sedation and dysphoria may also occur (Martin et al. 1971; Tecce and Cole 1974; Brown et al. 1978; Weiner 1980). This variation in response has been used by some investigators as a means to delineate subtyps of patients within diagnostic categories (Fawcett and Siomopoulos 1971; Janowski et al. 1973; Halbreich et al. 1981).

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Although PS drugs have a variety of medical and psychiatric uses, including the treatment of narcolepsy, pediatric and adult behavioral disturbances, autonomic and bronchospastic disorders (Rall 1980), they have also played an important role as pharmacologic probes for the purposes of diagnosis, prediction of clinical response and exploration of potentially relevant neurochemical mechanisms of mental syndromes (Angrist and vanKammen 1984). This review will focus on the use of PS drugs as pharmacologic probes in the study of patients with schizophrenia.

Chronic or sustained use of PS, specifically amphetamine, has been shown to induce a toxic psychosis closely resembling the acute symptoms of paranoid schizophrenia (Connell 1958; Angrist and Gershon 1970; Griffith et al. 1972; Bell 1973). This well established phenomenon has significantly contributed to the dopamine (DA) hypothesis of schizophrenia which holds that the psychotic symptoms of schizophrenia are produced by an overactivity of dopaminergic neurotransmission within the CNS (Snyder 1973; Meltzer and Stahl 1976). Although direct support of the DA hypothesis of schizophrenia is lacking, there have been several reports of increased DA and norepinephrine (NE) activity in schizophrenia (Haracz 1982; Hornykiewicz 1982). In recent years the DA hypothesis has undergone mechanistic revisions which have focused attention on receptor dynamics (Snyder 1976) and suggest a neurochemical basis for a subtype of schizophrenia (Crow 1980) and symptom constellations in schizophrenic pathology (Johnstone et al. 1978; Angrist et al. 1980a; Mackay and Crow 1980).

The rationale for a strategy utilizing PS as pharmacologic tools in schizophrenia is somewhat circular in that PS enhance the activities of catecholamine neurotransmitters and also that the psychotic symptoms of schizophrenia are believed to be mediated by catecholamine overactivity (Snyder et al. 1974). The major evidence for the latter concept comes from the observed psychotogenic effects of PS administration in normals (Angrist et al. 1974) and the fact that neuroleptic drugs' potency in blocking DA receptors parallels their clinical antipsychotic efficacy (Creese et al. 1976; Seeman et al. 1976).

Based on these findings, one would predict that PS would have an enhanced and distinct effect when administered to patients with schizophrenia. It must be emphasized that this phenomenon (psychotogenic effects of acute PS drug administration) is different in method, dose and timing from the gradual induction of a paranoid-like toxic psychosis from sustained use of amphetamine. What dis-

tinguishes the use of PS in a challenge paradigm are dosages that are *subpsychotogenic* in non-vulnerable, i.e., non-schizophrenic subjects.

Methods

Review criteria. Despite extensive applications in psychiatry, PS were not well conceptualized as pharmacologic probes until the seminal work of Janowsky et al. (1973) and Angrist et al. (1974). Prior to that they were used predominantly as pharmacologic treatment agents or as adjuncts to facilitate psychotherapy. While many of the earlier studies using PS differed conceptually and were limited by methodology and design, some were able to provide information relevant to evaluating PS response in schizophrenia. Therefore, we have included studies in this review that may not conform in rationale and design to the PS challenge paradigm. The minimal inclusion criteria for studies reviewed were:

1. Publication in English, French or German.
2. Subjects included adult patients with schizophrenia.
3. Sufficient description of study method and results to enable determination of patient response.

Each article was examined for the following elements: drug, dose and mode of administration; study rationale, hypothesis to be tested; study design, including whether a control group and control treatment were used; blind; randomization; description of sample, use of diagnostic criteria, clinical status of subjects (acute, chronic, remitted), medication status; subject response, method of response determination; conclusions. Patients were then classified by diagnosis and individual response rates were determined for each study. Drug response was classified as worse, improved or no change. In studies where sufficient information to determine individual patient response was not provided, we estimated response rates (where there was sufficient information to do so, e.g., "80% of subjects worsened") or classified by type of response that portion of the sample on which information was provided. The definition of response was that used by the study's authors. In those studies that did not define (with criteria) response or described it ambiguously, we defined it as follows: "worse" constituted a clinically significant deterioration in mental condition and behavior from the patient's pre-treatment status. For schizophrenic patients this included increased psychotic symptoms; for non-schizophrenic patients two designations were used: "worse" and "worse with psychotic symptoms". Simple worsening refers to behavioral responses that were subjectively and symptomatically adverse and included dysphoria, anxiety, agitation, emotional lability and somatic discomfort. Worsening with psychotic symptoms necessarily included the development or exacerbation of psychotic symptoms, e.g., hallucinations, delusions, thought disorganization, bizarre behavior. "Improved" constituted a decrease of mental symptoms and/or an improvement in behavioral function. "No change" was defined as no significant difference in mental condition or behavior from pre-treatment. For studies in which insufficient information was provided to estimate or determine individual patient response rates on a portion of the sample, no individual response rates were used and only the author's conclusions were recorded.

Methodologic considerations. Of the literature between 1937 and 1982, 36 studies were selected for review (Guttman and Sargant 1937; Schube et al. 1937; Anderson 1938; Flugel 1938; Woolley 1938; Belart 1942; Davidoff and Reifenstein 1939; Gottlieb and Coburn 1944; Gottlieb et al. 1945; Simon and Taube 1946; Delay 1949; Bischoff 1951; Hope et al. 1951; Liddell et al. 1953; Jonas 1954; Pennes 1954; Witton 1960a, b; Guile 1963; Lehmann and Ban 1964; Modell and Hussar 1965; Askar et al. 1970; Janowsky et al. 1973; Kiloh et al. 1974; Jankowsky and Davis 1976; Kornetsky 1976; Janowsky et al. 1977; vanKammen et al. 1977; Jankowsky et al. 1978; Levine et al. 1978; Angrist et al. 1980b; vanKammen et al. 1980; vanKammen et al. 1982a, b, c; Angrist et al. 1985). Design and methodology of the studies varied widely. As expected, studies done after 1970 were generally superior in methodology and design. However, the majority of studies had methodologic limitations. Since these factors can have a substantial effect on the response patterns of patients, several methodologic issues will be briefly considered.

Diagnosis and clinical status. Only 10 of the 36 (Janowsky et al. 1973; Janowsky and Davis 1976; Janowsky et al. 1977; vanKammen et al. 197; Angrist et al. 1980b; vanKammen et al. 1980; vanKammen et al. 1982a, b, c; Angrist et al. 1985) studies reported their method of diagnosis, e.g., nosologic scheme, operational criteria. Many of the studies did not provide sufficient clinical description of patients. Such factors as duration of illness, number of prior episodes and chronicity are relevant to pharmacologic response. The significant impact of heterogeneity on schizophrenia research has been previously discussed (Buchsbaum and Rieder 1979).

Medication status. In evaluating PS response it is important to know the medication status of subjects at the time of testing. Specifically, are patients receiving neuroleptics concomitantly? A critical factor in determining the presence of neuroleptics is length of the washout period. If the presence of a neuroleptic affects PS response, than residual drug could also alter the patient's response. This is particularly important in those patients who previously had been receiving long-acting injectable neuroleptics, as the half-lives of these drugs are longer (Tune et al. 1980; Merali and Toth 1982).

Mode of administration. Psychostimulants were administered in a variety of ways: orally for various lengths of time ranging from a single administration (Kornetsky 1976; Janowsky et al. 1978; Angrist et al. 1980b; Angrist et al. 1985) to daily doses repeated over various periods of time (Anderson 1938; Flugel 1938; Woolley 1938; Davidoff and Reifenstein 1939; Bischoff 1951; Liddell and Weil-Malherbe 1953; Witton 1960b; Kornetsky 1976); and parenterally by intramuscular, subcutaneous or intravenous administration, both as a single (Davidoff and Reifenstein 1939; Belart 1942; Simon and Taube 1946; Delay 1949; Hope et al. 1951; Liddell and Weil-Malherbe 1953; Jonas 1954; Pennes 1954; Guile 1963; Janowsky et al. 1973; Kiloh et al. 1974; Janowsky and Davis 1976; Janowsky et al. 1977; vanKammen et al. 1977; Janowsky et al. 1978; Levine et al. 1978; vanKammen et al. 1980, 1982a, b, c) and repeated (Schube et al. 1937; Flugel 1938; Davidoff and Reifenstein 1939; Gottlieb and Coburn 1944; Gottlieb et al. 1945;