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CLASSICS IN PSYCHIATRY

Akhil Anand, M.D.


Objective: To review a landmark study which was published in JAMA Psychiatry in 1988 that examined clozapine’s efficacy and adverse effects profile in treatment-resistance schizophrenia vs chlorpromazine.

Methods: This study was designed as a prospective double blind study that compiled data from sixteen centers. The initial pool of treatment resistant schizophrenics was 319. All patients in the pool, met the DSM-III criteria for schizophrenia and met a defined criteria as refractory to treatment which was either that patients were poor responders to three different antipsychotics (from at least two different chemical classes) or if patient had no period of good functioning with the preceding five years. Subjects also had to score at least a score of 45 in the total Brief Psychiatric Rating Scale (BPRS) and a minimum Clinical Global Impression scale of 4 to show the patient was actively moderately ill. To further confirm treatment refractory, all 319 patients also would first enter a prospective period of treatment with haloperidol (up to 60mg/d or higher) and benztropine mesylate (6mg/d) for a period of six weeks; any haloperidol responders were dropped from further study.

Patients who were unresponsive to the six week haloperidol trial would then be randomly assigned to a six week double blind treatment trial with either clozapine (up to 900 mg/d) or chlorpromazine and benztropine mesylate (up to 1800mg/d of chlorpromazine hydrochloride and up to 6mg/d of benztropine mesylate). Chlorpromazine was chosen, as it was a commonly used typical antipsychotic used at that time, similar adverse-effect profile (excluding the EPS symptoms which were treated prophylactically by Benztropine) and because of it low-potency profile for wider range dosing.

All patients would receive identical looking pills and a placebo white pill was given with clozapine to further enhance the blind. Patients were weekly evaluated for treatment response with BPRS and CGI, as well as nurses would regularly evaluate patient’s using the 30-item Nurses’ Observation Scale for Inpatient Evaluation (NOSIE-30). Regarding safety, titration was guideline based and regular clinical laboratory tests, physical exams and an electrocardiogram was done. To evaluate for extrapyramidal side effects, the Simpson Angus Scale for Extrapyramidal Side Effects and the Abnormal Involuntary Movements Scale (AIMS) were also done.

For patient to be defined as a post-treatment responder, the patient’s BPRS score was to decrease by a minimum of 20% plus a CGI score below 3 or a post-treatment BPRS score of 35 or less.

Results: Of the 319 patient pool, 80% completed the six week haloperidol trial and of these, 80% were non-responders, leaving a patient total of 268 that entered the clozapine vs chlorpromazine and benztropine double blind phase. The completion success for both the clozapine and chlorpromazine trials were 88% and 87% respectively; early termination occurred because of adverse reactions, other illnesses, uncooperativeness, exacerbation of symptoms and other reasons. Mean peak dosages
exceeding 1200mg/d of chlorpromazine and 600mg/d of clozapine, which are both considered therapeutic levels for both antipsychotics.

Regarding clinical efficacy, the improvement in both the BPRS score and CGI scale was approximately three times greater in the clozapine-treated patients; clinically significant data showed that clozapine was more efficacious than chlorpromazine from the first week of treatment initiation, all the way through the six week trial. Clozapine was noted to be more efficacious in resolving both positive and negative symptoms. The NOSIE-30 scale concurred with the results. Data was homogenous, as this outcome was seen in 14 of the 16 centers. Overall, it was found that only 4% of patients treated with chlorpromazine and benztropine had improved, whereas 30% of clozapine-treated patients had improved (P < .001).

Regarding safety, most common side effects for clozapine were drowsiness (21%), tachycardia (17%) and constipation (16%) vs chlorpromazine which were hypotension (38%), dry mouth (20%), and dizziness (16%). Not a single patient developed agranulocytosis on clozapine. Although benztropine was used to mask EPS symptoms in patients taking chlorpromazine, it was noted that the clozapine-treated patients had a significantly higher mean baseline score on the AIMS (8.8 vs 6.5).

**Conclusion:** This study concluded that clozapine to be superior to chlorpromazine and haloperidol for treating treatment-resistant schizophrenics both in resolving positive and negative symptoms. Data obtained was not only clinically significant but homogenous throughout the centers. It also concluded that given such a strong pool of patients (and strong completion rate), the likelihood of developing agranulocytosis or other lethal side effects when on clozapine in the first six weeks are also low.

**Punchline:** Landmark studies of the 80s have positioned Clozapine as the drug of choice for refractory schizophrenia.

**CONSULTATION LIAISON PSYCHIATRY**

Mohsina Ahmed, M.D.


**Objectives:** To present two cases of alcohol and sedative-hypnotic withdrawal catatonia, to provide a systematic review of the literature on cases of withdrawal catatonia and to summarize evidence for a potential relationship between withdrawal catatonia and withdrawal delirium.

**Methods:** Authors searched EMBASE, MEDLINE and PsychINFO databases for cases of withdrawal catatonia related to alcohol or sedative-hypnotic.

**Results:** Case(s): A 53 year old white male with history significant for decade long alcohol use disorder, alcohol detoxications and alcohol withdrawal delirium was admitted for alcohol withdrawal and pancreatitis. He was placed on symptom-triggered diazepam protocol. On hospital days 7, he developed agitation, mutism, staring, posturing, waxy flexibility, minimal oral intake with a Bush-Francis Catatonia Rating Scale (BFCRS) score of 14. He was treated with Diazepam 10 mg every 6 hours and placed on 5-day taper. His mentation and catatonic features showed marked improvement within 24 hours. Another case of a 62 year old white
female with MDD and unspecified anxiety disorder on Clonazepam 1 mg at bedtime (for 2 years), mild neurocognitive disorder, fibromyalgia, and history of gastric bypass surgery was admitted to short-term rehabilitation for altered mental status. She had been transferred from an outside hospital where she stayed for 8 days for lower extremity edema where her clonazepam and scheduled fentanyl were discontinued without them. She developed immobility, negativism, echolalia, verbigerations, and inability to speak spontaneously which persisted for 48 hours and she was transferred to a hospital. Her BFCRS score was 15. Clonazepam was restarted that within hours of receiving first dose her symptoms resolved without recurrence.

Authors found 26 cases of which 5 represented withdrawal from alcohol and 18 represented withdrawal from various sedative-hypnotic agents (benzodiazepines, zolpidem, and glutethimide). All cases presented with stuporous catatonia, average age was 56 years with roughly equal prevalence in men and women. Withdrawal catatonia is marked by mutism, negativism, immobility, withdrawal and other typical catatonic signs. It occurs only after prolonged use of alcohol or sedative-hypnotic agent. Similar to alcohol withdrawal delirium, catatonia features emerged within 3-7 days after discontinuation of alcohol or sedative-hypnotic. Both short and long half-life benzodiazepines appear to be associated with similar time to onset of catatonia. Both types of withdrawal catatonia appear to respond to benzodiazepines. Additionally, withdrawal catatonia and delirium appear to present without abnormal electroencephalographic (EEG) findings such as diffuse slowing.

**Conclusion:** Alcohol and sedative-hypnotic withdrawal can include catatonic features. Withdrawal catatonia and withdrawal delirium share natural history, pathophysiology, response to benzodiazepines or ECT, regular absence of abnormal EEG findings, and phenotypes. There is no conclusive evidence that withdrawal delirium is a variant of catatonia.

**Punchline:** *Catatonia can occur in the setting of alcohol- or benzodiazepine withdrawal and shares several features with withdrawal delirium.*

**GERIATRIC PSYCHIATRY**

**Rajesh Tampi, M.D.**


**Objectives:** The investigators wanted to study the reasons for why some family caregivers have difficulty in dealing with BPSD.

**Methods:** The investigators searched five electronic databases using a search strategy that combined medical subject headings and text words relating to dementia and BPSD. The studies were restricted to those in the English language that were published between 1980 and April 2012 and included data from family caregiver’s account of BPSD and/or the reasons why they felt these BPSD were challenging.

**Results:** The investigators found a total of 70 studies that met the inclusion criteria.
Withdrawal behaviors (apathy) were identified as being distressing for families. A lack of interest in information/activities reduced the range of shared pleasurable activities. Repetitive interactions and a sense of declining conversation worsened the distress associated with BPSD and were appraised as being challenging. Deteriorating communication with the relative was perceived as distressing and difficult to cope with by the family caregivers and therefore appraised as being ‘challenging’. When conversation and shared activities declined the caregivers missed the companionship. This sense of loss of the person they once knew when acute, resulted in grief when the caregivers appraised their loved one as ‘not knowing or recognizing them’.

Repeated questioning about ‘forgotten’ tasks or activities by the individual with dementia that required the caregiver to constantly repeat requests was perceived as being challenging.

Accusations of stealing made by the individual with dementia when interpreted as being aggressive and personally offensive were perceived as stressful.

The personal expectations of caregivers and their own need for care due to any reason appeared to affect the thresholds of tolerance for BPSD.

BPSD that caused embarrassment and shame for the caregivers in public were also perceived as being very stressful.

The sense that individuals with dementia invariably lose their identity to the illness was perceived as being challenging for the family caregivers.

Conclusions: The investigators concluded that family caregivers find BPSD as being challenging when there is a sense of declining relationship with the individual with dementia, a perceived loss of personhood by the individual with dementia and when behaviors are perceived as being transgressions of social norms.

Punchline: This systematic review indicates that BPSD causes a lot of distress to family caregivers of individuals with dementia. Clinicians caring for individuals with BPSD should routinely enquire about the psychological health of caregivers give the distress caused by the BPSD.

Rajesh Tampi, M.D.


Objectives: The investigators wanted to study the association between neuropsychiatric syndromes and global clinical deterioration in individuals with AD.

Methods: The cohort for the study included 156 individuals with AD. Probable AD was diagnosed according to the NINCDS-ADRDA criteria. The clinical diagnosis of dementia was also made using the DSM-IV TR criteria. The dementia severity was assessed using the MMSE, the Clinical Dementia Rating (CDR), the Pfeffer Functional Activities Questionnaire and the Global Deterioration Scale (GDS).
The individuals with AD were classified using the CDR into mild (CDR 1), moderate (CDR 2) and severe stage (CDR 3).

The neuropsychiatric syndromes were assessed using the Neuropsychiatric Interview (NPI).

Neuropsychiatric syndromes were classified into five syndromes including: psychosis (delusions, hallucinations); agitation (agitated behavior, aggression, disinhibition, irritability, euphoria, aberrant motor behavior, aberrant vocalizations); affective disorder (depression, anxiety); apathy (indifference, apathetic symptoms, appetite eating disorders); and sleep disorders (night-time behavior disturbances).

The investigators calculated the correlation between the neuropsychiatric syndromes and the GDS according to dementia severity levels (CDR 1, 2, and 3).

**Results:** The investigators found that for the total sample, apathy and agitation syndromes were highly correlated with clinical deterioration according to the GDS. This was followed by psychosis, affective syndromes and by the sleep disorders syndrome.

They also found that the agitation syndrome significantly correlated with mild and moderate dementia (CDR 1 and 2). At CDR 2 (moderate dementia), agitation and affective syndromes were most strongly correlated with clinical deterioration. At CDR 3 (severe dementia) the apathy syndrome was most strongly correlated with clinical deterioration.

**Conclusions:** The investigators concluded that agitation, apathy and affective syndromes were most strongly correlated with global clinical deterioration among individuals with AD.

**Punchline:** This study adds further proof that neuropsychiatric syndromes especially agitation, apathy and affective symptoms are most strongly correlated with global clinical deterioration among individuals with AD.

Rajesh Tampi, M.D.

**Study:** van Schoor NM, Comijs HC, Llewellyn DJ, Lips P. Cross-sectional and longitudinal associations between serum 25-hydroxyvitamin D and cognitive functioning. Int Psychogeriatr. 2016 May;28(5):759-68.

**Objectives:** The investigators wanted to examine the cross-sectional and longitudinal associations between serum 25-hydroxyvitamin D (25(OH) D) level and cognitive functioning in older adults.

**Methods:** The sample for the study included individuals who were ≥55 years in age who were drawn from the population registers of eleven municipalities of three regions in the Netherlands. A total of 3,107 individuals were enrolled in the baseline examination in 1992/93. The measurements including the main interview and a medical interview were repeated every three years. For the present study the participants had to have had their medical interview in 1995/96 and were to be born on or before 1930. The MMSE was used as a screening test for general cognitive functioning. The Raven’s Colored Progressive Matrices (RCPM) a non-verbal/visual test was used to measure a person’s ability of non-verbal and abstract reasoning. Memory performance was measured with an abbreviated version of the Auditory Verbal Learning Test (AVLT). Information processing speed was measured by an adjusted version of the Alphabet Coding Task 15. The morning blood samples were obtained in 1995/96 and the serum
25(OH) D levels were determined using a competitive protein binding assay which was completed in 1997/1998.

**Results:** Individuals having lower serum 25(OH) D levels were significantly older and more often women when compared with individuals having higher serum 25(OH) D levels. Their blood was sampled more often in the winter, they had lower levels of education, had more depressive symptoms, were less active and consumed more alcohol.

For the cross-sectional analyses in a fully adjusted model for age, sex, season of blood collection, educational level, presence of depressive symptoms, heart sease, diabetes, hypertension, alcohol use, smoking and physical activity, a serum 25(OH) D level < 30 nmol/L was associated with lower general cognitive functioning and a slower information processing speed when compared to individuals having serum 25(OH)D levels ≥ 75 nmol/L. For general cognitive functioning and slower information processing speed the optimal cut-off for serum 25(OH)D was about 60 nmol/L.

For the longitudinal analyses in the fully adjusted models, there were no statistically significant associations noted between cognition, processing speed and 25(OH) D levels.

**Conclusions:** The investigators concluded that a lower serum 25(OH) D level is associated with lower general cognitive functioning and slower information processing speed but not with a faster rate of cognitive decline in older individuals.

**Punchline:** This study adds to the growing body of literature that lower serum 25-hydroxyvitamin D level is associated with lower general cognition and slower information processing speed in older adults.
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