9 Psychotic Exercerbation With Neuroleptic Medications: A Case Report

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Abstract
Case reports of 4 psychotic patients managed by the researcher's team at the University of Ilorin Teaching Hospital were presented. There were observed deterioration of clinical conditions with increasing dosages of haloperidol in the cohorts, but remarkable improvement when chlorpromazine was substituted for haloperidol. There was neither evidence of gender difference nor family history of mental illness in the cases, but there was associated severe extra-pyramidal symptoms (EPS).
Possible reasons for the observation were discussed and preventative measures were advanced.

Keywords: Psychotic Exacerbation.

Introduction
Despite the fact that neuroleptics are the main biological treatment for psychotic disorders, they sometimes could aggravate the symptoms of psychoses (1-3). In some cases, aggravations occur with withdrawal of neuroleptics and may occur early in the interruption of treatment (2,4). In some other cases, aggravations occur during the course of treatment with increasing dosages of neuroleptics. Several hypotheses have been advanced for these developments and one of such hypothesis was the 'concept of supersensitivity'(2) while another attributed these to the possibility of the existence of 'therapeutic window' property with neuroleptic medications (1).
Antipsychotics have been reported to be effective at a threshold concentration or therapeutic concentration range, above which, dose escalation is of no benefit to patients (5).
Exacerbation of clinical conditions in patients being treated with antipsychotics had been reported with haloperidol, lithium, and tricyclic antidepressants (1,3,6-8), and these patients were reported to be characteristically of female sex, history of brief onset of illness, family history of affective disorder, and severe neuroleptic side effects (7).
Neuroleptic psychoses due to over-prescription or over-treatment of the mentally ill patients have been a bit under-reported in this environment compared with cases of toxic psychoses following abuse of other agents like sedatives, and antidiarrhea (9). This paper reports 4 cases managed by the author's team at the University of Ilorin Teaching Hospital.
Case 1
B. S. is a 43 years old Muslim widow, a trader who presented to the Accident and Emergency department with 5 days history of pain in the neck muscles and headache, generalized tremulousness, inability to open her mouth or talk and excessive salivation. Seven months before presentation, she had attacked her brother-in-law, accusing him of plotting to kill her, and her children, and in the process, destroyed his car's windscreen. She was then brought to the GOP department where she was seen and commenced on tabs. haloperidol 5mg tds, and benzhexol 2.5mg tds.
There was past history of psychiatric illness about 6 years prior, characterized by undue quarrelsomness, abusiveness, undue aggression, and accusing neighbours and relatives of plotting against her. She was also hearing voices of unseen people discussing her. Because she was then able to attend to her business, no medical intervention was sought.
There was no family history of mental illness. Her early childhood history was not available but got married about 28 years prior and is the 4th wife of her husband and had 5 children. Her husband died in 1997.
Her mental state examination revealed a middle aged woman who was conscious and alert, coherent and cooperative. She appeared stiff with sardonic facie, fine tremor and no perceptual disturbances but had paranoid delusion and was insightless. She was assessed to have chronic schizophrenia in partial

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remission with severe extrapyramidal symptoms (EPS) and the tab. haloperidol was reduced to 5mg bd, and tab. benzhexol increased to 5mg tds. After 1 week on admission, she was still insightless, with no improvement in rigidity and tremor. By mid second week, 100mg of chlorpromazine was introduced and the haloperidol reduced to 5mg nocte. Over the subsequent 2 weeks, haloperidol was tailed off, and tab. Chlorpromazine was increased to 100mg-150mg-150mg and this was followed by markedly reduced rigidity and tremor, as well as marked melting of the paranoid delusion. Patient was discharged home by the end of the 4th week on tabs chlorpromazine 150mg bd, 200mg nocte and benzhexol 5mg tds. At discharge, all EPS symptoms had disappeared, paranoid delusion completely melted, she could recount her symptoms, and became insightful. She had since remained stable.

Case 2

A.J. is a 14 years old female secondary school student, Christian by religion who presented at the Emergency paediatric unit with a 3-day history of generalized abdominal pain associated with intermittent high grade fever, chill and rigor. There was no diarrhea or vomiting. At about the same time, parents noticed she was reading the bible for most of the day and calling on Jesus to deliver her. She was also claiming to be seeing spirit-like beings by her bedside in clear consciousness, as well as hearing voices of unseen people in clear consciousness, and were muttering incomprehensible words to her, all of which made her afraid. She responded to questions in the manners that did not have bearings with issues being discussed. There was no previous history of similar illness and neither was there any family history of mental illness.

Mental state examination revealed a young girl, clinging to her mother, appeared apprehensive and trying to strip naked. She denied perceptual disturbances but her behaviour was suggestive of somebody having visual and auditory hallucinations. Her speech was of normal stream, though demonstrated echolalia. She was orientated to time, place and person. The immediate and short-term memory were poor, attention and concentration were poor, and she was insightless. On physical examination, she was febrile with axillary temperature of 38.7°C. Assessment was that of Acute organic brain syndrome.

She was being managed by the paediatricians for possible Typhoid septicaemia, and was on antibiotics. Laboratory investigations (full blood count, erythrocytes sedimentation rate, malaria parasites, urine analysis, blood culture) were also ordered. She was then commenced on tabs. haloperidol 2.5mg bd, and benzhexol 2.5mg bd, and by the 18th day on admission, the fever and abdominal pains had subsided but the psychopathologies persisted. She was then transferred to the psychiatric ward and the tabs. haloperidol and benzhexol were increased to 5mg tds, and 5mg bd, 2.5mg nocte, respectively. She however, did not show any remarkable improvement as she was still apprehensive, very restless, shouting and exhibiting behaviours that were suggestive of both visual and auditory hallucinations. After a week, the tab. haloperidol was further increased to 5mg bd, 7.5mg nocte but by the middle of the week, she had developed marked EPS with rigidity, tremulousness and excessive salivation as well as persisting psychopathology. The tab. haloperidol was then withdrawn at this pointand tab chlorpromazine introduced at 50mg bd, 100mg nocte, and tab benzhexol increased to 5mg tds. Within a week of this adjustment, the hallucinations had disappeared, posturing and echolalia subsided, and she became less restless, but still rigid. The tab. chlorpromazine was subsequently reduced to 50mg tds, and was discharged 2 weeks later on tabs. chlorpromazine 25mg bd, 50mg nocte, while all the EPS had disappeared, had gained full insight, and was back to her pre-morbid level of functioning. She had remained stable on follow-up visits.

Case 3

O. J. is an 18 years old Muslim male, secondary school student on referral by the GOP department and brought to the outpatient psychiatric clinic by the parents with one-week history of suspicion of smoking hemp and snuffing glue, 4-day history of wandering out of the house, disrespectful to parents and siblings, poor sleep, talkativeness and laughing to self, and talking irrationally.

His parents suspected he might be smoking cannabis and sniffing glue because about one-week earlier, he had left the house and on his return about 6 hours later, the parents noticed his eyeballs were reddened and rude in both speech and behaviour towards the parents when they enquired about his where-about. This necessitated his being scolded by the elder siblings during which he confessed of having sniffed a chemical he had bought for =N=20:00, which he tied to the sleeve of his shirt from where he sniffed it. The elder siblings identified the chemical to be glue. He admitted smoking cannabis

He admitted smoking cannabis but refused to disclose when he started. His sleep pattern had been poor before presentation, and was talkative, giving inappropriate answers to questions. He talked and laughed to self and did not possess any special power or ability nor being unduly happy or energetic. He had not been feeling unduly sad, easily fatigued or expressing hopelessness, worthlessness or suicidal ideation..

About 6-month prior, he was seen at the General Outpatient Department (GOPD) with history of talking and laughing to self and behaving as if conversing with unseen persons. He was also restless, pacing up and down the house, not engaged in any constructive activity whatsoever. At times, he would tell his parents that people in pictures and calendars hung on the wall of the house were speaking to him. On another occasion, he would pack his clothes into the dustbin claiming they were old. He was then commenced on tabs. chlorpromazine, haloperidol, and benzhexol (doses were not known) on outpatient basis for almost 4-months, with some levels of improvement but exhausted the drugs about a week before this presentation at the psychiatric Out-Patient clinic.

There was no family history of mental illness. While in Senior Secondary level, he had joined the gang of bad boys and started playing truancy, calling the bluffs of his teachers, and beating up schoolmates. At home, he refused to partake in household chores, going out at will and often caught smoking cigarettes. His academic performance began to drop and he failed promotion examination to Senior class III. He refused to continue with schooling until the parents changed his school and by the second term in the new school, he had started exhibiting bad habits and this led to complete stoppage of school. There was however no history of contact with the law enforcement agents.

On mental state examination, he was fairly kempt, with labile affect, rapid and incoherent speech. He was easily distractible and could not be engaged in any meaningful discussion. Assessment then was that of substance-induced psychosis. He was commenced on tabs. haloperidol 5mg-10mg-10mg, benzhaxol 2.5mg tds. The tabs. haloperidol was increased over 3 weeks to 15mg tds, and benzhexol to 5mg tds during which period the patient showed some levels of improvement (talking/laughing to self became less, more restful and coherent). In the 4th week, the tab. haloperidol was increased to 15mg bd, 20mg nocte but there was worsening of psychopathology by the middle of the 4th week, with more incoherence in speech, talking and laughing to self. A further addition of 5mg of tab. haloperidol at the beginning of the 5th week did not bring about any desirable change but instead started having serious extra-pyramidal side effects (EPS) (rigidity, hypersalivation). By the end of the 5th week, tab. chlorpromazine 100mg nocte was introduced and haloperidol decreased to 15mg tds with the aim of tailing it off. By the end of the following week, with tab. chlorpromazine at 250mg nocte and haloperidol reduced to 20mg bd, there was noticeable clinical improvement (talking/laughing to self became less, speech more comprehensible and the EPS much reduced). The tab. chlorpromazine was steadily increased over 3 weeks period to 300mg bd, 400mg nocte, and tab. haloperidol completely tailed off, with continuing clinical improvement. Patient was discharged home 2 weeks later on tabs. chlorpromazine 300mg 400mg 400mg, and benzhexol 5mg 2.5mg 2.5mg having fully recovered (full insight, complete resolution of psychopathologies and the EPS). He had since remained well on follow-up.

Case 4

A. T. is a 20 years old single male Arabic teacher resident in Okebo in Ikirun, Osun state and presented at the OP clinic with a 2 week history of poor sleep, talkativeness, feeling of self importance, restlessness, dancing and singing alone, and undue irritability. There was no family history of mental illness. He had formal education up to primary 6 and later attended Quranic school where he graduated as a Quranic teacher.

His mental state examination was that of a well-groomed and kempt young man, appeared irritable and uncooperative. His mood could not be assessed but the affect was labile. There was commanding auditory hallucination, fast speech but not pressured, with loosening of association, and grandiosed idea (claimed to be a prophet and could decree things to happen). The cognitive functions were intact but the judgement was poor and he was insightless. There was no abnormality on his physical examination. He was treated as a schizophrenic illness and commenced on OP treatment due to lack of bed space, with im fluphenazine decanoate, 25mg stat (because of his uncooperativeness and insightlessness), tabs. haloperidol 10mg tds, chlorpromazine 50mg nocte, and benzhexol 2.5mg tds. He was given 1 week follow-up appointment but failed to honour it until 4 weeks later whence he then presented with talkativeness, restlessness, wandering tendency, singing and crying, talking and laughing alone with deteriorating personal hygiene, all were said to have started barely a week after the last visit.

His mental state examination then revealed a fairly groomed young boy with sad mood, blunt affect, commenting and commanding auditory hallucinations. His speech was loosened, had poor judgement and was insightless. His physical examination revealed no abnormality. He was then admitted into the ward and recommenced on tab. haloperidol 5mg tds which was later reviewed upward to 5mg-10mg-10mg, and tab. chlorpromazine 100mg nocte was introduced on the 6th day of admission due to poor sleep and restlessness. He also had im fluphenazine decanoate 25mg stat. He was observed to be stiff on the 7th day of admission and tab benzhexol 2.5mg tds was recommenced which was increased to 5mg tds on the 13th day and tab haloperidol increased to 10mg-15mg-15mg. Further increment in the dose of haloperidol was made on day 16, to 15mg tds and on day 23, to 15mg bd, 20mg nocte, because of persistent psychopathologies. He was noticed to be weepy and hypersalivating on day 30, and tab chlorpromazine was reduced to 50mg nocte which was discontinued on day 37, and tabhaloperidol increased to 15mg-20mg-20mg with further increase to 20mg tds on day 48, with a consideration for discharge if he remained stable.

On day 51 of admission, patient was noticed to be restless with hypersalivation and auditory hallucination. It was then decided to substitute tab. haloperidol with chlorpromazine. This was commenced gradually with tab
chlorpromazine 200mg tds, and tab. haloperidol reduced to 10mg bd, 20mg nocte. On day 76, patient showed some improvement, and with subsequent adjustment of medications to tab. chlorpromazine 300mg-400mg-400mg, and tab. haloperidol to 5mg-10mg-10mg, there was marked improvement as evident by the disappearance of EPS and restlessness. He was eventually discharged on day 79 having returned to his pre-morbid level of functioning on tab. chlorpromazine 400mg-500mg-500mg, tab. haloperidol 10mg nocte, and tab. benzhexol 5mg tds. The tab haloperidol was eventually withdrawn on the first follow-up visit and had since remained stable.

Discussion

Various adverse reactions have been reported with neuroleptics and these may include extrapyramidal side effects like dystonias, neuroleptic malignant syndrome, and worsening of psychosis (1, 6-8,10-12). This development had been attributed to several factors. For instance, the central (e.g. depression, elation, hallucination, and delirium) anticholinergic properties of neuroleptics and anti-parkinsonian agents have been implicated in the causation or exacerbation of psychoses (1,6,9). Bowers, et al (7) in a case study of a group of psychotic patients on antipsychotics reported worsening of their clinical conditions early in the treatment. The affected cohorts were reported to be characteristically of female sex with relatively brief onset of illness, family history of affective disorder, and severe neuroleptic side effects.

All the 4 cases presented have further laid credence to this possibility of exacerbation of psychotic symptoms with neuroleptic medication, in this case, haloperidol. This was in conformity with previous studies that have implicated
haloperidol in the causation of such exacerbation(1,6-8). Possible reasons previously advanced for this problem was increased anticholinergic properties, supersensitivity, and the low therapeutic window of neuroleptics(1,2,6).

Because majority of the cases in this report demonstrated severe extrapyramidal side effects (EPS), it confirmed the findings of previous studies (10,11) that reported severe EPS as being relatively common in patients with exacerbation. It however partially defers from previous study (7) on the issue of brief history of illness because only about 50% of the cases had history of brief illness ranging between 2 days to 2 weeks. It was also not in agreement with the reports that exacerbation was commoner in female patients, and those with family history of affective disorder (7), because none of the cohorts had family history of mental illness, and the gender distribution was about equal.

These cohorts manifested deteriorations in their clinical conditions and no sooner the antipsychotic medications (haloperidol) were switched over to chlorpromazine than they began to show clinical improvement. We therefore report that haloperidol could have exacerbated psychosis in these cohorts possibly as a result of overneuroleptization during the course of treatment. It is unclear however, whether the concurrent administration of other neuroleptics (fluphenazine and chlorpromazine) caused increased anticholinergic property, this may need further study. Other possibilities could be due to drug interactions, and inherent biological factors in the cohorts. All these could be subjects of further research.

Nevertheless, these observations have thrown up certain lingering and
debatable issues in this environment, such as:

(a) overzealousness in management - in as mach as clinicians desires quick response of patients, one must not loose sight of the possibility of over-management or over-neuroleplization, with the

attendant non-response or worsening of clinical conditions, and problem with compliance following discharge. Antipsychotic therapy should aim at relief of symptoms without the introduction of adverse effects or serious adverse events, improved quality of life, cost effectiveness, and a positive long-term outcome. Studies have shown non-compliance to be a major factor contributing to the low effectiveness of antipsychotic therapy (13-16) and this could be influenced by factors like drug types and formulations, cost of treatment and barrier to treatment, medication side effects, patient, disease status, physician, healthcare system, community care and family;

(b) The concept of "therapeutic window" in neuroleptic medications (1,6,7); and

(c) The need to encourage the use of atypical neuroleptics in this environment.

Some of the recently introduced antipsychotics have been shown to be more effective in certain clinical situations and to have a more favourable adverse effect profile than the classical antipsychotics (13).

University of Ilorin Teaching Hospital (UITH) enjoys patronage from the neighbouring towns of Oyo, Ogbomoso, Osogbo, and Minna which are characteristically of low socioeconomic standard compared to more urbanized cities like Lagos. Perhaps, because the newer (atypical) antipsychotics may be more expensive, the psychiatrists in these areas more often than not may be constrained in their day-to-day prescriptions because these patients might not have sufficient financial capabilities for expensive drugs.

Nevertheless, when the desired clinical improvement is not seen after having waited long enough (perhaps 4-6 weeks of therapeutic trial) or emergence of side effects or exacerbation, trying other neuroleptics, especially, the newer (atypical) ones that have been proven to have lesser side effects and high effectiveness may be worthwhile (17,18).

The indigenous pharmaceutical companies (and their marketers) need to be encouraged to produce (and distribute) these newer drugs at affordable prices for these economically-disadvantaged population.

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