

When and How to Withdraw or Reduce the Long-Term
Maintenance Anti-Psychotic Medication for Chronic
Schizophrenic Patients. A Research Strategy.

TOSHINORI KITAMURA, MD, MRCPsych, PhD

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I.

It is usual in clinical practice to maintain anti-psychotic medication once it is started for patients diagnosed as suffering from schizophrenia. It is invariably believed that the ever progressive process of the illness can be suppressed by long term medication and that when it is discontinued the patients are likely to relapse. This notion has been supported by several investigations which have demonstrated that the discontinuation of the maintenance antipsychotic treatment is more often than not followed by relapses of acute exacerbation of schizophrenia. ¹⁻⁷⁾

A work done by Prien et al.⁸⁾ is worth noting here as its example. They replaced real antipsychotic medication with placebos for stabilized chronic schizophrenics. About 60% of the patients relapsed within 6 months after the discontinuation of active medication. Of particular interest to the present discussion is the fact that the relapse rate depended on the total dose of medication calculated by chlorpromazine equation. This finding has been interpreted that the schizophrenic process, which is masked, if not cured, by higher doses of medication, is more "malignant" than that suppressed by lower dose. The former patients therefore are more likely to relapse when becoming free from real medication.

From this and other research works there is now little doubt that schizophrenics should be kept on maintenance anti-psychotic medication for indefinite time period in order to prevent them from further relapses. ⁹⁾ Since an obstacle for the maintenance therapy of chronic schizophrenia is a low compliance of patients' drug taking, partly due to lack of insight, the main concern of clinical psychiatrists has been how to keep their patients on medication without disruption. A development of long acting depot injections of phenothiazines such as fluphenazine decanoate ¹⁰⁻¹⁸⁾ and flupenthixol decanoate ¹⁹⁾ is on this line and they have been in clinical use for the past decade in many countries. ²⁰⁾

II.

Despite its initial enthusiasm, the long term anti-psychotic medication has recently been re-evaluated critically.

Firstly, the other side of the coin of Prien et al.'s study⁸⁾ quoted before is that 40% of the patients maintained on neuroleptics remained stable even 6 months after the replacement with placebos. For these 40% of the patients, the drug administration seems useless and should be avoided. These cases can be deemed to be "benign" schizophrenia. The label of schizophrenia can not be a sentence of indefinite anti-psychotic medication. A drawback of this argument is, however, that little has known which patients belong to which group, "malignant" or "benign", though many clinical investigations

have been trying to disentangle this issue.²¹⁻³⁰⁾

Secondly, it has gradually been recognised that anti-psychotics, whether phenothiazines or butyrophenones, can only work on acute episodes of psychosis whilst chronic symptoms are often hard, if not impossible, to be alleviated by chemotherapy.³¹⁾

Thirdly, much evidence has been accumulated for the hypothesis that long term anti-psychotic medication leads to hypersensitivity of dopaminergic (DA) post-synaptic receptors.^{32,33)} Patients with hypersensitised DA receptors are very likely to manifest acute symptoms when their medication is abruptly stopped. Hypersensitivity psychosis is a coined term to describe this condition.³⁴⁾ If this is the case, the anti-psychotic medication for those with good prognosis has to be discontinued once they pass through the acute stage of the illness.

Furthermore DA hypersensitivity may have potential dangers to cause a variety of physical side effects which may arise as rebound phenomena following the discontinuation or reduction of antipsychotic agents.³⁵⁻³⁷⁾

Fourthly, side effects of long term neuroleptics, such as tardive dyskinesia³⁸⁻⁴³⁾ and clouding of cornea are usually, if not always, irreversible.

All in all, the therapeutic benefits of long term antipsychotic medication are very likely to coincide with adverse effects of the therapy.

III.

If one can distinguish schizophrenics with good prognosis from those with poor one and those who have been benefited by neuroleptics from those who have not, then it can be determined which patients can and should become free from medication.

Much light has been shed to the psychopathological aspects of this issue without a definite conclusion. In the present essay, a biochemical strategy to solve this problem will be considered.

The patients discussed in this article will be those who have been on neuroleptic medication for a considerably long time and who have been relatively free from marked psychotic symptoms. They may be outpatients or in-patients. These subjects will be divided into a few categories through some biochemical measurements and it will be seen if this categorization is useful in identifying the therapeutic efficacy and predicting the occurrence of relapses as well as physical side effects.

The strategy adopted here is to measure blood prolactin level as the indicator of the central nervous system DA activity and to measure blood drug level as the indicator of drug efficacy. The working hypothesis is summarised in Table 1.

Table 1.

Group	Drug level	PRL level	Hypersensitivity	Management
I	low	low	absent	Reduce or withdraw medication
II	high	low	present	Reduce the dose carefully and gradually
III	low	high	absent	?
IV	high	high	absent	?

In Group I in Table 1, the blood level of prolactin is low. So is the drug level. The prolactin level is low since there is virtually no circulating neuroleptic. This does not cause anti-DA activity. There is no room for DA hypersensitivity to occur. The Group I patients who have been free from psychopathology for a considerably long time with low drug level may be regarded as those with good prognosis. The neuroleptics for them can, therefore, be safely withdrawn.

The Group II manifests a low prolactin level despite a high (i. e. therapeutic) level of the medication. This may be a reflection of the DA hypersensitivity of the central nervous system. Those patients are not benefited much by medication but are likely to manifest either hypersensitivity psychosis or physical side effects quoted above. The withdrawal of medication should be regarded as a contraindication. Even reduction of the dose of the medication should be done with great care.

The Group III is characterised by a high prolactin level and a low drug level. A feasible interpretation for this group is that the DA receptors are blocked by exceptionally small amount of medication.

The Group IV is probably the most usual situation where both the blood level and the prolactin level are satisfactorily high. Here the DA receptors are blocked but not hypersensitized.

For both Group III and IV, one can only assume that the medication has therapeutic effects on the patients. It is as yet not known whether the medication can and should be withdrawn since there is no clue as to whether these patients belong to good or poor prognostic schizophrenia.

IV.

A research design which can be derived from the above hypothesis is as follows.

The ideas described here can be applied for chronic schizophrenic patients who have been completely or partially remitted on the maintenance doses of neuroleptics. In some stage of the course of treatment, the blood prolactin level and the blood drug level will be measured, so that the patients can be allocated into the four subcategories.

A first strategy is the follow-up of the patients who have been and will be on the same therapeutic regimen. What is to be expected is a high rate of relapses or side effects (such as tardive dyskinesia and physical troubles) of the Group II patients as compared to the other three.⁴⁴⁾

A second strategy is the reduction or replacement of the real medication. If all the sample patients are given placebos, then one can expect that the rate of relapses or side effects is lower for the Group I patients as compared with the other three. The rate of relapses or side effects of the Group II is expected to be higher than the other groups.

Thirdly, if drug/prolactin ratio is an indicator of hypersensitivity, then one should explore the critical point of this ratio, the value above which is most likely to be associated with relapses or side effects.

V.

The above hypothesis has been constructed on the assumption that all the DA receptors of the central nervous system manifest the same degree of activity and that these receptors can be equally inhibited by the same DA blockers. This is, however, too simplified an argument.

Although the level of prolactin is mediated exclusively by DA activity,⁴⁵⁾ it has been claimed that prolactin reaches its "ceiling" by a dose of neuroleptics which is much lower than that of usual therapeutic effects.⁴⁶⁾

Nevertheless, Gruen et al.⁴⁶⁾ correlated the prolactin level with the oral dose of the medication but not with the blood drug level. There is ample evidence that the correlation of oral dose of medication with its blood level is poor.⁴⁷⁻⁵⁰⁾ Yet Itoh et al.⁵¹⁾ demonstrated a linear relationship between the blood level of haloperidol and the prolactin level. This is presumably because oral medication in some cases can not lift the blood level of the drug over a certain critical level, which is below its usual therapeutic level. This is indirectly supported by a study done by Kolakowska et al.⁵²⁾ who injected haloperidol into schizophrenic patients with conventional oral neuroleptics and who found that prolactin level can be elevated. It is therefore feasible to regard the prolactin level as an indicator of therapeutic effects of neuroleptics.

There are at least three DA pathways pertinent to the present discussion, namely nigrostriatal, tuberoinfundibular, and mesolimbic. The first is the locus of extrapyramidal side effects of the neuroleptic treatment including Parkinsonian syndrome in the acute stage and tardive dyskinesia in the chronic stage of the treatment; the second is the locus of the control of the pituitary hormones, one of which is prolactin. Prolactin is, unlike the other pituitary hormones, exclusively under the control of DA. The third DA pathway, mesolimbic, is thought of as the locus of psychopathological symptoms. These pathways should be interpreted as discrete and independent on each other.

Recent biochemical investigations have subcategorized DA receptors into several subgroups, making the whole view more complicated to tackle.^{53,54)}

Nevertheless, most neuroleptics in current use are pervasive DA blockers. They have potentials to elicit not only extrapyramidal side effects but to lift up the prolactin level and to alleviate psychotic turmoils. Kolakowska and Wiles⁴⁷⁻⁵⁰⁾ showed a significant correlation between the extrapyramidal side effects and the prolactin level of those treated by chlorpromazine. It is therefore very likely that when one group of DA receptors is blocked by a neuroleptic agent, another will be also blocked to a similar degree by the same medication. When one group is hypersensitized by a long term medication, another may well be hypersensitized too.

A second assumption which the present hypothesis rests on is the definite therapeutic blood level of neuroleptics. Little is known about this, and further studies remain to be done. An extremely low blood level of a drug can be, however, thought of as exhibiting no therapeutic effects.⁵⁵⁾ The critical level of the drug is to be determined through the projects suggested here.

In everyday practice psychiatrists tend to prescribe many agents at one time. What has to be done to provide sufficient number of "pure" patients who have been on the same and single medication, is to refrain from polypharmacy. If, however, this can not be done, radioreceptor assay⁵⁶⁾ may well become an excellent alternative for the assessment of the blood drug level.

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慢性精神分裂病患者に対する抗精神病薬維持療法 終結の時期決定—研究戦略

慶応義塾大学医学部精神神経科学教室 北村俊則

精神分裂病患者においては急性期を経た後も、再発防止のため抗精神病薬を維持投与することが一般的になっている。しかし何割かの患者においては維持抗精神病薬を中止しても再発を認めないことから、維持療法が必ずしも全例に必要なことは明らかである。しかしどの症例がどちらの群に属するかについては、臨床精神病理学的研究が多いにもかかわらず成果をみていない。

そこでこの問題に対する生物学的検討のひとつとしてここでは血中プロラクチン濃度と抗精神病薬の血中濃度の測定を軸にした研究戦略を提唱する。前者を中枢神経系のドーパミン活性の指標とし、後者を抗精神病薬の活性の指標とするものである。

維持療法中の患者も血中プロラクチン濃度及び抗精神病薬濃度の高低により4群に分ける。すなわち第1群は低プロラクチン、低抗精神病薬、第2群は低プロラクチン、高抗精神病薬、第3群は高プロラクチン、低抗精神病薬、第4群は高プロラクチン、高抗精神病薬によって特徴づけられるものとする。

この4群の中で、ドーパミン受容体の過感受性が第2群には出現すると予想され、また第1群は良好な予後を呈する群と思われる。そのため維持療法を継続しても、再発あるいは遅発性ジスキネジアなどの副作用の出現の可能性の高いものは第2群であり、更に維持療法中止により再発あるいは副作用の最もきたしにくいのは第1群であると思われる。