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Original Research

The impact of fluphenazine withdrawal: a mirror-image study

S. Meehan[1], S. Moran[1], A. Rainford[1], C. McDonald[1,2] and B. Hallahan[1,2]

[1]School of Medicine, University of Galway, Galway, Ireland and [2]Galway-Roscommon Mental Health Services, University Hospital Galway, Galway, Ireland

Abstract

Background: Fluphenazine decanoate licenced as a long-acting injectable (LAI) first-generation antipsychotic (FGA) was withdrawn from sale in 2018. This study evaluates if its withdrawal resulted in increased relapse rates of psychosis in an Irish patient cohort and examines which prescribed alternative antipsychotic medications were associated with more optimal outcomes.

Methods: Fifteen participants diagnosed with a psychotic disorder were included. A mirror-image study over 24-months' pre-and post-withdrawal of fluphenazine was conducted. Kaplan-Meier survival and proportional hazards analyses were conducted. The impact of alternate antipsychotic agents (LAI flupenthixol compared to other antipsychotic medications) was evaluated. Semi-structured interviews with participants examined subjective opinions regarding the change in their treatment.

Results: Seven participants (46.7%) relapsed in the 24-month period subsequent to fluphenazine discontinuation compared to one individual (6.7%) in the previous identical time-period ($p = 0.035$). Flupenthixol treatment was associated with reduced relapse rates compared to other antipsychotics ($\chi^2 = 5.402$, $p = 0.02$). Thematic analysis revealed that participants believed that the discontinuation of fluphenazine deleteriously impacted the stability of their mental disorder.

Conclusion: The withdrawal of fluphenazine was associated with increased relapse rate in individuals previously demonstrating stability of their psychotic disorder. While acknowledging the limitation of small sample size, preliminary evidence from this study suggests that treatment with the first-generation antipsychotic (FGA) flupenthixol was associated with a lower risk of relapse compared to SGAs. Reasons for this lower risk of relapse are not fully clear but could be related to dopamine hypersensitivity with this treatment change.

Keywords: Fluphenazine; first-generation antipsychotic (FGA); relapse of psychosis; schizophrenia

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Introduction

Fluphenazine decanoate is a first-generation antipsychotic (FGA) agent (most common brand name is Modecate) belonging to the phenothiazine class of antipsychotic medications. Fluphenazine was introduced in 1959 (Matar et al., 2013) and was withdrawn from Ireland and other countries in 2018 due to manufacturing difficulties with the active pharmaceutical ingredient (Movsisyan et al., 2019). Fluphenazine was licenced for use as an antipsychotic medication for patients with psychotic disorders including schizophrenia, schizoaffective disorder, delusional disorder and bipolar affective disorder (Health Products Regulatory Authority 2018; Siragusa et al., 2023).

Several FGA antipsychotic medications have been withdrawn from production over the last 20 years, including most recently the perphenazine in its' long-acting injectable (LAI) formulations (Leucht, et al., 2021). The most high profile withdrawal of an antipsychotic medication was thioridazine (oral formulation) due to concerns related to cardiac arrhythmias on a phased basis from 2001 to 2005, with a significant increase in relapse rates and hospitalisations secondary to same noted (Purhonen et al., 2012). Pipotiazine palmitate a LAI, FGA was withdrawn in 2015, and was similarly associated with an increase in relapse rates (Sheldon et al., 2022).

LAI antipsychotic agents including fluphenazine have repeatedly demonstrated superiority over their oral equivalent medications and are usually prescribed to increase adherence rates and consequently have frequently in observational studies (but not randomised controlled trials (Schneider-Thoma et al., 2022) where there is greater equivalence in terms of participant selection and support) demonstrated reduced relapse rates of psychosis (Kishimoto et al., 2014; Marcus et al., 2015). Currently, there is no clear evidence of which alternate treatment might be optimal on an individual level. Thus, in this study we wanted to determine relapse rates for individuals who discontinued fluphenazine decanoate due to its withdrawal from the Irish market. Additionally, we wanted to ascertain if any antipsychotic agent prescribed post-discontinuation of fluphenazine (i.e. FGA v second-generation antipsychotic (SGA)) was associated with reduced relapse rates over the course of 24 months. Finally we wanted to attain subjective opinions from participants to understand their experience of this change in their psychotropic medication.

Corresponding author: B. Hallahan; Email: brian.hallahan@universityofgalway.ie

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Methods

Study design

A 24 month mirror-image design compared relapse rates in the 24-months prior to- compared to the 24-months post- discontinuation of fluphenazine. A relapse of psychosis was defined as (i) hospital readmission, (ii) the development of psychotic symptoms (i.e. delusions or hallucinations) where none previously existed or (iii) an increase in psychotic symptoms more than the patient's usual perturbations, requiring significantly increased input from the treating community mental health team. A relapse of psychosis was diagnosed based on clinical note review and discussions with the participants treating mental health team (consultant psychiatrist and community mental health nurse(s)).

All participants were adults and attended the Galway-Roscommon Mental Health Services. Exclusion criteria included participants with an intellectual disability (IQ < 70), dementia, an inability to consent to study participation, or if not treated with fluphenazine for at least 24-months prior to discontinuation of this medication. Prospective participants were identified via an email distributed to the various community treatment centres and staff within the Galway mental health services.

Data were gathered over a three-month period (April 1st – June 30th, 2023). Demographic and clinical data were gathered from participants' clinical files (after informed written consent was attained). Quantitative data included diagnosis, age, gender, the presence of a psychotic relapse, adverse effects of fluphenazine or newly prescribed alternate antipsychotics, years of illness, and duration of fluphenazine decanoate usage.

In addition to quantitative data, qualitative data was gathered via semi-structured interviews with patients to gain insight into their subjective experiences pertaining to the discontinuation of fluphenazine (see Appendix A).

Data was analysed using the Statistical Package for Social Sciences (SPSS) 27.0 for Windows (SPSS Inc., IBM, New York, USA) and R Studio (version 4.2). Descriptive analyses (percentages, standard deviations, and means) on key demographic and clinical data (including relapse rates) were attained. Chi-square analysis (or Fisher's Exact test as appropriate) determined rates of relapse pre- and post-fluphenazine discontinuation, differential impact of treatment with flupenthixol compared to other antipsychotic agents post-discontinuation, and impact of psychotic disorder on relapse rates. Kaplan-Meier survival analyses were conducted to investigate time to relapse in the 24-month period after switching from fluphenazine and if treatment with a FGA or SGA affected time to relapse. Logistic regression was undertaken to ascertain if predictor variables (primary diagnosis, years of stability, age, gender, and alternative treatment to fluphenazine (FGA v. SGA)) influenced relapse rates. A Cox proportional hazards regression analysis was conducted to examine the relationship between the predictors of time to relapse and risk of relapse.

Qualitative data involved semi-structured interviews by telephone (see Appendix A). Free-text data attained were examined and open-coded based on the framework of the questionnaire and on any other themes unrelated to these questions that emerged. This data attained from free texts was then grouped into themes by consensus of the researchers (SM, BH).

Table 1. Demographic and clinical variables

		Statistics
	n (%)	χ^2, *p*
Gender (female)	10 (66.7)	
Diagnosis		
Schizophrenia	11 (73.3)	
Schizoaffective disorder	3 (20.0)	
Bipolar disorder	1 (6.7)	
Comorbid diagnoses		
Obsessive compulsive disorder	2 (13.3)	
Alcohol use disorder	2 (13.3)	
Occupational status		
Unemployed	12 (80.0)	
Retired	2 (13.3)	
Employed	1 (6.7)	
Initial treatment change		
FGA		
Flupenthixol LAI	9 (60.0)	
SGA		
Paliperidone LAI	1 (6.7)	
Paliperidone OAP	2 (13.3)	
Olanzapine po	1 (6.7)	
Increased dose of amisulpride	1 (6.7)	
Increased dose of olanzapine	1 (6.7)	
Relapse rates		
24-months prior to fluphenazine withdrawal	1 (6.7)	6.14, 0.035*
24 months after withdrawal of fluphenazine	7 (46.7)**	
	Mean (SD)	***t, p***
Age	64.9 (8.4)	
Years of stability	11.6 (6.3)	
Fluphenazine weekly dose	21.7 (15.2)	
Chlorpromazine equivalence dose	436.7 (301.4)	

LAI, Long-acting injectable.
*Fisher's exact test.
**One participant required a voluntary inpatient admission to a psychiatric inpatient unit.

Results

Of the 23 individuals invited to participate, 16 (69.6%) provide written informed consent, with one additional individual excluded (treatment with fluphenazine for too brief a duration). Demographics and clinical details pertaining to participants are provided in Table 1, with 10 participants of female gender (66.7%) and 11 participants diagnosed with schizophrenia (73.3%). Thirteen participants (86.7%) were commenced on another antipsychotic medication, including nine participants (60.0%) who were commenced on the LAI FGA flupenthixol, with both individuals who were treated with a second antipsychotic as an augmentation agent

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Table 2. Antipsychotic treatment over 24 month follow-up period

Participant	1st Antipsychotic	Treatment change
1	Flupenthixol (LAI)	–
2	Flupenthixol (LAI)	–
3	Flupenthixol (LAI)	Olanzapine (po)
4	Flupenthixol (LAI)	–
5	Flupenthixol (LAI)	–
6	Paliperidone (LAI)	Flupenthixol (LAI)
7	Paliperidone (LAI)	Olanzapine (po)
8	Amisulpride (po)	Dose increased
9	Flupenthixol (LAI)	–
10	Flupenthixol (LAI)	–
11	Paliperidone (LAI)	Paliperidone (po)
12	Quetiapine (po)	Flupenthixol (LAI)
13	Olanzapine (po increased)	Risperidone (LAI)
14	Flupenthixol (LAI)	–
15	Flupenthixol (LAI)	–

po, per oral; LAI, Long-acting injectable.

Table 3. Cox regression model of time to relapse

Predictor	β	Hazard ratio	p
Model 1: New treatment type (FGA/SGA)	1.68	5.38	0.07
Years of stability	−0.06	0.94	0.56
Schizophrenia	−1.51	0.22	0.30
Schizoaffective Disorder	−2.44	0.09	0.18

initially having the dose of this existing antipsychotic increased (see Tables 1 and 2).

Seven participants (46.7%) experienced a relapse in the 24 months after fluphenazine discontinuation, with three of these relapses experienced within the first 6 months post-withdrawal compared to one participant (6.7%) who experienced a relapse of psychosis in the 24 month time-period prior to the withdrawal of this medication ($p = 0.035$). The risk of relapse was lower for individuals switched to the LAI FGA flupenthixol compared to other antipsychotics ($\chi^2 = 5.402$, $p = 0.02$), with an effect size of 0.60 (Cramer's V). Dose of fluphenazine or chlorpromazine equivalents did not differ between individuals who experienced or did not experience a relapse of psychosis (Table 1). A regression analysis conducted including years of stability, age, antipsychotic medication (FGA v SGA) and gender as predictor variables, and relapse as the outcome variable noted only a trend for antipsychotic medication type ($\beta = 3.91$, $p = 0.09$) (Table 2). A Cox regression model conducted to assess the predictors of time to relapse (antipsychotic (FGA/SGA), years of stability, and primary diagnosis (schizophrenia, schizoaffective disorder or bipolar disorder)) noted a non-significant effect only for medication type (hazard ratio of 5.38, $p = 0.07$, Table 3).

All six participants who were initially not prescribed flupenthixol experienced a relapse of psychosis with only one of these participants remaining on their initial medication (dose increased) with their relapse ameliorating without requiring a change of antipsychotic medication. Two of the other six participants were switched to flupenthixol LAI (Table 2). All participants, attained stability by the end of the study period.

Box 1. Thematic Data from qualitative interviews

Theme 1: Deleterious impact on overall mental well-being

- 'My sleep was poorer, and I had more anxiety with new treatment initially' [#08, oral antipsychotic]
- 'With the new treatment, I have increased tremors of my hands and legs. This was less severe with Modecate'. [#03, flupenthixol]
- 'With my new treatment I am more forgetful and have poorer concentration'. [#13, oral antipsychotic]
- 'I felt very agitated after the change in medication' [#06, LAI SGA]

Theme 2: Fear that treatment change would lead to a relapse of psychosis

- 'I would have preferred to stay as I was' [#02, oral antipsychotic]
- 'In the long-term, it worked out well, but I found the process of trying a different medication difficult and I was concerned I would relapse' [#05, flupenthixol]

Theme 3: No concerns evident

- 'They are both the same, I have noticed no difference'. [#01, flupenthixol]
- 'With the new drug I now feel more energised' [#05, flupenthixol]

Eight participants (53.3%) agreed to engage in semi-structured interviews pertaining to their experience of discontinuing fluphenazine. Themes that emerged included: 1) a deleterious impact of discontinuing fluphenazine on overall mental well-being (including increased anxiety and reduced concentration), 2) a fear that a change in treatment would lead to a relapse of psychosis and 3) no concerns (see Box 1).

Discussion

In this study, we provide evidence that the withdrawal of fluphenazine from sale in Ireland had a deleterious impact on individuals with established psychotic disorders, causing relatively high rates of relapse (47%) in individuals who previously exhibited long-standing stability of their mental disorder. Preliminary evidence also supports that treatment with another LAI FGA (flupenthixol) rather than an oral medication or a SGA reduced the risk of relapse post-fluphenazine discontinuation.

Relapse rates noted in this study are consistent with studies evaluating previous FGA antipsychotics that have been withdrawn from production. One study (of low numbers) evaluated fluphenazine discontinuation due to market withdrawal in Australia (2017) and noted that four out of nine patients (44.4%) relapsed and required admission to an acute psychiatric inpatient unit (Zanker and Ferraro 2017). As previously stated, the withdrawal of other FGA antipsychotics has also led to increased risk of relapse, including most notably thioridazine (only available via oral formulation) (Purhonen et al., 2012), but also the FAI LAI pipotiazine (Sheldon et al., 2022).

Given the recent trend for removal from production of LAI FGAs, treatment strategies to reduce relapse rates are required. In the current study, the FGA flupenthixol administered via LAI was associated with reduced relapse rates and historically, flupenthixol has demonstrated a similar albeit not identical therapeutic effects (Johnson and Malik 1975; Wistedt and Ranta 1983, Ostuzzi et al.,

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2021) perhaps explained by subtle pharmacological differences (flupenthixol has a nitrogen atom replaced by a carbon atom compared to fluphenazine (Poulsen et al., 2021)). Another potential reason for higher relapse rates with SGAs compared to FGAs is their comparatively lower potent dopaminergic blockade. Flupenthixol is pharmacodynamically similar to fluphenazine with similar potent antagonism at D2 receptors (Reimold et al., 2007). Indeed, both fluphenazine and flupenthixol bind more tightly than dopamine to the D2 receptors ($K < 1$) unlike the SGAs ($K > 1$) prescribed in this study (olanzapine, quetiapine, amisulpride) (Seeman 2002). Relapses of psychosis have been muted to be related to neuro-adaptations that persist after cessation (or reductions) in dopamine 2 antagonistic antipsychotics). The withdrawal of dopamine antagonistic antipsychotics (i.e. FGAs), result in sensitised dopamine receptors exposed to physiological levels of dopamine (Chouinard et al., 2017), potentially leading to increased dopaminergic activity in pathways associated with psychosis including associative striatal pathways (McCutcheon et al., 2019). Adaptations to antipsychotic exposure have been purported to persist for many months or years after stopping antipsychotics, and consequently tapering of antipsychotics and in particular highly potent dopamine 2 antagonists (i.e. fluphenazine) has been suggested to require a very gradual process (Horowitz et al., 2023).

In addition to SGAs potentially being less effective in reducing relapse rates, it is possible that partial treatment non-adherence (not noted by patients or in their clinical records) played a role in participants' relapse. Consistent evidence demonstrated clinical superiority in relation to relapse rates of LAIs compared to oral administration, even when the same antipsychotic medication is prescribed in different forms (Schooler 2003; Tiihonen et al., 2017; Tiihonen et al., 2006).

Free-text data (albeit limited) noted for many participants a deleterious impact on their overall mental well-being with a preference that no treatment change had occurred. Fluphenazine was withdrawn due to manufacturing issues and not due to inefficacy or adverse events. It is possible that withdrawals of other FGAs will result in relapse but potentially not if patients are switched to alternative FGAs. Future studies evaluating an enforced change in antipsychotic medications should consider the addition of a qualitative arm to ascertain the subjective impact of such a change given the current dearth of such research.

This study has a number of limitations. The most significant of these is the small sample size, however this is the largest such study to date and demonstrates consistent findings with studies that have examined the withdrawal of other FGAs. No psychometric measurements of psychotic symptoms (i.e. positive and negative syndrome scale) were undertaken, and thus quantification of the change in specific or overall symptomatology including non-psychotic symptoms such as anxiety were unattainable. Whilst all participants stated treatment adherence with their alternate antipsychotic medication, no definitive measure (i.e. serum blood levels) were undertaken to ascertain this. A notable strength of this study is that the trigger for a treatment switch was the unavailability of fluphenazine rather than an episode of illness, which has been a source of bias in some mirror-image study designs.

Conclusion

The withdrawal of fluphenazine was associated with increased relapse rate in individuals previously demonstrating stability of their psychotic disorder with many participants stating a preference that no treatment change had occurred. While acknowledging the limitation of small sample size, preliminary evidence from this study suggests that treatment with the first-generation antipsychotic (FGA) flupenthixol was associated with a lower risk of relapse compared to other SGAs. Reasons for this lower risk of relapse are not fully clear but could be related to dopamine hypersensitivity with this treatment change.

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Ethical standard. Ethical approval was attained from the Galway University Hospitals Research Ethics Committee (C.A.2445). The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committee on human experimentation with the Helsinki Declaration of 1975, as revised in 2008.

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Appendix A: Questions for participants

1. How do you feel about the change of your medication from fluphenazine to your new medication?
2. Did you previously experience side effects with fluphenazine?
3. Do you experience side effects with your current medication?
4. Did you experience side effects with any other medication you switched to when fluphenazine was stopped?
5. Which of these medications is better from a side effect perspective (fluphenazine or other medications)
6. Do you think that changing medication from fluphenazine has affected your mental health? Please explain this?
7. Would you have preferred if your medication had not changed from fluphenazine?

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