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# **Pharmacological Lactation Suppression with D<sub>2</sub> Receptor Agonists and Risk of Postpartum Psychosis: A Systematic Review.**

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**Pharmacological Lactation Suppression with D<sub>2</sub> Receptor Agonists and Risk of Postpartum Psychosis: A Systematic Review.**

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**Abstract**

**Background:** It has been suggested that D<sub>2</sub> receptor agonists commonly used postpartum for the physiological suppression of lactation, such as bromocriptine and cabergoline, may increase the risk of illness onset or relapse in women where there is a predisposition for, or history of schizophrenia, bipolar disorder or postpartum psychosis. This is based on two lines of reasoning: current models of psychosis assume episodes are triggered by dysregulation of brain dopaminergic activity and treated by medications that universally have D<sub>2</sub> receptor antagonist properties; and limited research suggesting these agents may be associated with psychotic episodes in vulnerable individuals outside of the postpartum period.

**Aim:** To examine whether D<sub>2</sub> agonists trigger psychosis in previously well mothers, or psychotic relapse or exacerbation of symptoms in mothers with known psychotic illnesses, when used to suppress lactation during the early postpartum period.

**Materials and Methods:** A systematic review of the literature was undertaken of electronic databases including: MEDLINE, EMBASE and PsychINFO from 1950 to 2015 using the keywords.

**Results:** 8 case reports, 3 case series and a pharmacovigilance survey were identified.

**Conclusion:** Whilst D<sub>2</sub> receptor agonists appear to increase the risk of triggering psychosis in previously well mothers and those previously diagnosed with schizophrenia, bipolar disorder and postpartum psychosis bromocriptine appears to pose a much greater risk than cabergoline. When considering the use of pharmacological agents to suppress lactation physicians should carefully screen patients for a history of psychosis and consider alternatives in order to moderate this risk.

### Introduction

The World Health Organization gives a clear recommendation that breastfeeding is the preferred option for infant nutrition and should be supported exclusively for 6 months and partially up until 2 years of age. However, only 38% of infants are exclusively breastfed globally from 0 to 6 months of age <sup>1</sup>. There are a range of individual and societal reasons and rates vary across nations. However, for women with schizophrenia, bipolar disorder or a history of postpartum psychosis the choice to breastfeed is more complex as it is influenced by both the illness and its treatment. For instance, there is evidence that suggests that the sleep deprivation associated with breastfeeding during the early postpartum may increase the risk of psychotic relapse for women with bipolar disorder or a history of postpartum psychosis, and pharmacological agents such as lithium and clozapine are considered potentially incompatible with breastfeeding. In addition, there are women with serious mental illnesses who require lactation suppression following neonatal loss or child removal by protective services.

In order to prevent breast engorgement, leakage of milk, discomfort and pain, a range of non-pharmacological and pharmacological options exist to aid lactation suppression. Non-pharmacological means include: tight brassieres or binders, minimizing nipple stimulation, ice packs and cabbage leaves. Pharmacological options mainly involve ergot derivative medications that are dopaminergic D<sub>2</sub> receptor agonists such as bromocriptine and cabergoline. These medications have established indications for both pathological and physiological hyperprolactinaemia. Pharmacological agents prescribed

in this context are used not to treat pathology, but to suppress an undesired normal physiological reaction. In this context pharmacological suppression of lactogenesis should generally be considered optional rather than a medical necessity, and a number of concerns have been raised regarding the practice.

The first Cochrane systematic review assessing the effectiveness of all forms of treatments for lactation suppression found the evidence was based on small trials of low methodological quality <sup>2</sup>. They conclude that there is weak evidence for pharmacological or non-pharmacological lactation suppression in the first week postpartum.

Additionally, debate regarding the safety of bromocriptine in particular has existed since the 1980s when concerns were raised about cardiovascular and neurological risks. The manufacturers of bromocriptine withdrew its use for lactation suppression in the US in 1994 following a series of adverse events including 9 deaths. The FDA has since recommended that medication not be used to suppress lactation, however the practice continues internationally.

Contemporary pathophysiological models of severe psychotic forms of mental illness (such as schizophrenia and bipolar disorder) assume that they are triggered by a dysregulation of dopaminergic activity in the brain arising from the adverse interaction of predisposing risk genes and environmental factors <sup>3</sup>. What all successful pharmacological treatments of psychosis have in common is an ability to act as dopamine D<sub>2</sub> receptor antagonists. This naturally raises the question as to whether patients with psychosis, or at risk of psychosis, are susceptible to onset or exacerbation of psychosis when they are prescribed D<sub>2</sub> agonists.

The early postnatal period represents a high-risk period for psychotic illness onset or relapse. Women are approximately 22 times more likely to experience the onset of a manic or psychotic episode in the first postpartum month than at any other time in their lives and the prevalence of postpartum psychosis in the general population is estimated as 1-2 per 1,000 deliveries <sup>4</sup>. A Danish population-based registry study found a relative risk of 5 for hospital admissions in women with a diagnosis of schizophrenia within the first postpartum month <sup>5</sup>. Women with a diagnosed bipolar disorder are at extremely

high risk of affective psychosis in the early postnatal period <sup>6 7</sup> and experience a nearly sevenfold higher risk of admission for a first episode and a nearly twofold higher risk for a recurrent episode when compared with non-postpartum and non-pregnant women <sup>8</sup>. The most important predictors for postpartum psychosis are a personal or family history of bipolar disorder or previous episode of postpartum psychosis. However, whilst women with bipolar disorder or schizophrenia are recognized to have an elevated risk of relapse during the early postnatal period, a significant portion of women who experience postpartum psychosis have no previous history of prior episodes <sup>8</sup>. The underlying pathophysiological mechanisms are poorly understood, however alterations in oestrogen levels and inflammatory processes, and fluctuations in biorhythms and functioning are currently under investigation.

Given that psychosis onset or relapse has been associated with dysregulation of brain dopaminergic activity and this risk appears greater during the early postpartum period it needs to be considered as to whether lactation suppression with D<sub>2</sub> agonists increases this risk.

First we need to examine whether there is any evidence that D<sub>2</sub> agonists precipitate psychosis onset or relapse when used to treat pathological processes. The primary indications for the use of ergot derivatives such as bromocriptine and cabergoline are for pathological hyperprolactinaemia (i.e. prolactinomas). They have also been used in Acromegaly, Parkinson's Disease, Restless Leg Syndrome, and amenorrhea and galactorrhoea secondary to neuroleptic use <sup>10</sup>. The main difference between the two agents is their duration of action and degree of dopamine receptor selectivity. When used to suppress physiological postpartum lactation bromocriptine is traditionally given as 2.5mg twice daily for 14 days and cabergoline (which has greater D<sub>2</sub> selectivity and longer half-life) as a single dose of 1mg. When used to treat pathological hyperprolactinaemia the doses tend to be higher and used for a prolonged period of time and in a comparison study the latter medication has been shown to have a lower incidence of adverse effects overall <sup>11</sup>.

In a study of 600 patients treated with the D<sub>2</sub> agonists bromocriptine and lisuride for functioning pituitary tumours at lower dosage eight developed medication-induced psychosis <sup>12</sup>. What is notable is that all of the eight had either a pre-existing history of

psychosis or displayed considerable changes in behaviour or mood prior to initiation of therapy. There have also been numerous case reports of patients treated with ergot derivatives developing a psychotic illness as a direct consequence of exposure to these agents when treated for pathological hyperprolactinaemia and other non-postpartum indications<sup>13 14 15</sup>. It is unclear if these cases represent cases of ergotism (a medication side effect)<sup>16</sup>, or whether the medication uncovered an underlying predisposition to psychosis. Further case reports suggest that these agents may trigger relapse or symptom exacerbation in patients with an established psychotic illness<sup>17 18</sup> or trigger a first episode of psychosis in predisposed individuals<sup>19 20 21</sup>. Once again, bromocriptine appears to be implicated more than cabergoline. The main problem with such case reports is that they are anecdotal and do not report on long-term outcome.

There has been some interest in the use of dopamine agonists in the treatment of neuroleptic induced hyperprolactinaemia<sup>22</sup>. An 8-week randomized, single-blind, placebo-controlled, multicentre study of 60 treated women with schizophrenia found that none experienced an exacerbation of their symptoms when bromocriptine was introduced in order to treat neuroleptic-induced hyperprolactinaemia<sup>23</sup>. Similarly, a pilot study of 19 patients with schizophrenia given cabergoline over a 6-week period to treat neuroleptic-induced hyperprolactinaemia found none had a worsening of their psychopathology<sup>24</sup>. This finding has been supported by other case and case series studies<sup>25 26 27</sup>. There appears to be only one report in the literature of cabergoline induced psychotic exacerbation in two schizophrenic patients when used to treat neuroleptic induced hyperprolactinaemia<sup>28</sup>.

Overall, the risk of D<sub>2</sub> agonists precipitating the onset or relapse of psychosis appears to be related to the drug, the indication, the dose and the individual.

### Aims

This systematic review aims to examine whether D<sub>2</sub> agonists trigger psychosis in previously well mothers, or psychotic relapse or exacerbation of symptoms in mothers with known psychotic illnesses, when used to suppress lactation during the early postpartum period.

### Methods

A systematic review was undertaken of electronic databases including: MEDLINE, EMBASE and PsycINFO which were searched for articles published between 1950 and December 2015 using the terms “bromocriptine”, “cabergoline”, “ab lactation”, “lactation suppression” and “psychosis”. Studies were eligible if they were original case reports, case series or cohort studies. In addition, manual searches of the references of included articles and review of the bibliographies of reference books and review articles was undertaken. Studies in languages other than English were translated using an online program prior to analysis and inclusion in the review. There were no exclusion criteria.

## Results

The systematic review of the literature identified 8 case reports, 3 case series, and a pharmacovigilance survey<sup>29 30 31 32 33 34 35 36 37 38 39 40</sup>. Most reports were of women experiencing a postpartum psychosis following prescription of bromocriptine for lactation suppression during the early postpartum period. These women had either been previously well or experienced a relapse or exacerbation of an underlying mood disorder or schizophrenia. Two studies reported that women with schizophrenia experienced no deterioration in psychotic symptoms following administration of bromocriptine in the early postpartum period. A French pharmacovigilance study for the period 1994 to 2010 reported nine cases of acute psychiatric illness potentially associated with lactation suppression using bromocriptine. Four cases were reported as puerperal psychosis, two as deterioration of schizophrenia, two as confusion and one as mania. There has only been one report of cabergoline triggering an episode of mania in a patient with a pre-existing psychotic illness and none in well women. Results are summarised in Table 1.

## Conclusion and Clinical Recommendations

Whilst both bromocriptine and cabergoline have been associated with triggering postpartum psychotic illness onset, relapse or exacerbation it has been proposed that the latter medication confers a lower risk.<sup>41</sup> This view is supported by this systematic review of the literature. The apparent lower incidence of cabergoline induced psychosis, when compared with bromocriptine, may reflect the benefits of its greater receptor specificity, lower overall exposure given the single dose regimen, or the fact that as a newer agent it has been subjected to a briefer time of post-release surveillance.



The literature identified within this systematic review has a number of limitations. In particular, there is a relatively low level of evidence as the bulk of research consists of case reports or case series. The sole randomized control trial was performed outside of the setting of parturition and lactation, and therefore may not be applicable to the perinatal context. There is insufficient evidence available to allow clinicians to quantify individual risk based upon the severity of a woman's pre-existing illness, the antipsychotic agent she is already prescribed or its dose at the time of treatment. It would be important for future studies to examine these issues.

Despite the absence of prospective double blind randomised trials there is enough evidence from these identified studies to suggest that caution be applied when prescribing lactation suppressants to women who have a personal or family history of psychotic illness, and particularly if the illness has previously had a postpartum onset or exacerbation. Cabergoline, with its greater dopaminergic selectivity appears to offer a lower risk of precipitating psychosis than bromocriptine and therefore would be the preferred agent if pharmacological suppression is indicated for an individual woman.

In conclusion, when considering the use of pharmacological agents to suppress lactation physicians should carefully screen patients for a personal as well as family history of schizophrenia, bipolar disorder and postpartum psychosis. Given the potential risk of psychotic relapse these agents may confer it is recommended that pharmacological lactation suppressants be avoided when there is a personal or family history of bipolar disorder or postpartum psychosis and used only with caution in patients with treated schizophrenia. In this context it is also important to note the overall limited evidence for their efficacy to suppress physiological lactation and the availability of viable non-pharmacological treatments. When a risk: benefit analysis is being performed it should also be considered that lactation suppressants used in the context of physiological lactation are not being used to treat pathology, but are used to assist with postpartum breast comfort and thus may be considered to be optional rather than essential. If a decision is made to prescribe lactation suppressants, then close monitoring of the patient's mental state is recommended.

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| Study                             | Design                    | Medication and number of subjects           | Findings                                                                                                                     |
|-----------------------------------|---------------------------|---------------------------------------------|------------------------------------------------------------------------------------------------------------------------------|
| Kemperman 1987 <sup>29</sup>      | Case report               | Bromocriptine<br>n = 1                      | Postpartum mania occurring in a woman with no pre-existing psychiatric illness                                               |
| Lake 1987 <sup>30</sup>           | Case report               | Bromocriptine<br>n = 1                      | Postpartum mania in a woman with a premorbid diagnosis of cyclothymia                                                        |
| Durst 1990 <sup>31</sup>          | Case series               | Bromocriptine<br>n = 2                      | Deterioration in mental state in 2 women with pre-existing psychosis following bromocriptine administration for ab lactation |
| Olbrich 1994 <sup>32</sup>        | Retrospective case series | Bromocriptine<br>n = 4                      | No postpartum worsening of psychosis in 4 women with a diagnosis of schizophrenia                                            |
| Reeves 1997 <sup>33</sup>         | Case report               | Bromocriptine<br>n = 1                      | Postpartum psychosis in a woman with no pre-existing psychiatric history                                                     |
| Canterbury 1989 <sup>34</sup>     | Retrospective case series | Bromocriptine<br>n = 2                      | Postpartum psychosis in a woman with no prior psychiatric history                                                            |
| Iffy 1989 <sup>35</sup>           | Case report               | Bromocriptine<br>n = 1                      | Postpartum psychosis in a woman with no premorbid psychiatric history                                                        |
| Pinardo Zabala 2003 <sup>36</sup> | Case report               | Bromocriptine<br>n = 1                      | Postpartum psychosis in a woman with no known psychiatric history                                                            |
| Misdrahi 2006 <sup>37</sup>       | Case report               | Bromocriptine<br>n = 1                      | Postpartum psychosis in a woman with a diagnosis of mood disorder                                                            |
| Gahr 2011 <sup>38</sup>           | Case report               | Cabergoline<br>n= 1<br>Bromocriptine<br>n=1 | A woman with schizophrenia treated serially with cabergoline then bromocriptine with no worsening of psychotic symptoms      |

|                                      |                             |                                                                |                                                                                                                                                                                                                                                                                                                                                     |
|--------------------------------------|-----------------------------|----------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Salinas Botran<br>2013 <sup>39</sup> | Case report                 | Cabergoline<br>n= 1                                            | Precipitation of postpartum<br>mania in a woman with a<br>history of psychosis                                                                                                                                                                                                                                                                      |
| Bernard 2015<br><sup>40</sup>        | Pharmacovigilance<br>Survey | 105 Severe<br>adverse events<br>reported with<br>Bromocriptine | Among women prescribed<br>bromocriptine for ablactation<br>there were reports of 9<br>psychiatric adverse events: 2<br>women with acute<br>deterioration of<br>schizophrenia, 4 with<br>postpartum psychosis, 2 with<br>confusion and 1 with mania.<br>There were also 5 reports of<br>“other nervous system<br>disorders” without<br>clarification |