ABSTRACT

The use of neuroleptics, especially risperidone, and their common side effect of hyperprolactinemia and the rare but significant adverse effect of gynecomastia has become a contentious issue. Advertisements for class action lawsuits and media reports of gynecomastia cause concern for patients and parents of children prescribed such medicines. The relationship between neuroleptic use, hyperprolactinemia, and gynecomastia is poorly understood, and there is very little guidance for psychiatrists, especially child psychiatrists, who need to prescribe these medicines. Although risperidone ranks high among atypical neuroleptics in producing hyperprolactinemia, unlike what many legal advertisements claim or suggest, no direct connection has been established between hyperprolactinemia and gynecomastia. Prescribers of risperidone and other neuroleptics would benefit from becoming more aware of the issue of neuroleptic-induced hyperprolactinemia and gynecomastia to avoid adverse effects for patients and ethical and legal jeopardy for themselves. This article presents facts and suggests measures that may be helpful for those prescribing risperidone and other neuroleptics, especially for children. [Psychiatr Ann. 2015;45(4):204-206, 208-211.]
The occurrence of gynecomastia in some children, adolescents, and adults who are treated with risperidone has become a contentious issue that has spawned conflicts, controversies, and legal actions. Apart from individual lawsuits against physicians prescribing risperidone, several class action lawsuits are presently being advertised in the media, soliciting those who have been prescribed Risperdal (risperidone) (Janssen, Titusville, NJ) and parents of minors who have been prescribed this medicine to join in these legal actions. Advertisements for such legal actions often erroneously claim or imply that hyperprolactinemia, which often occurs with use of risperidone and other neuroleptics, causes gynecomastia. The company that initially produced Risperdal has settled lawsuits filed by some states’ attorney generals accusing it of false marketing practices, but these lawsuits were not related to the occurrence of gynecomastia. In children and adolescents, it occurs frequently as a natural phenomenon (physiologically gynecomastia), mainly during the neonatal period and puberty. Pubertal gynecomastia can last for 6 to 12 months and then spontaneously regress in 95% of cases. It is distinguished from physiologically gynecomastia, which is an enlargement of breast tissue due to accumulation of fat, often in obese individuals.

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In addition to physiological gynecomastia, gynecomastia can also occur due to secondary causes, such as being induced by legal or illegal drugs or due to certain pathological conditions. The conditions most relevant in children are hypogonadism from causes such as mumps, hyperthyroidism, and conditions such as Klinefelter’s syndrome in which 80% of the children affected may exhibit gynecomastia.

About 30% to 60% of normal pubertal boys are reported to develop some degree of gynecomastia, depending on the definition of gynecomastia used. The commonly accepted definition is enlargement of subareolar breast tissue to a diameter of at least 2 cm. Drug-induced gynecomastia is estimated to occur in as few as 4% in some studies to as high as 25% in others. The high variability in the incidence of gynecomastia in various studies is mostly the result of disparity in criteria used to diagnose gynecomastia.

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schizophrenia and bipolar disorder in children, and later for treatment of “irritability” in children with autism. Since its introduction, risperidone has been one of the most widely prescribed and studied neuroleptics in the United States and other countries. In the past two decades, psychiatrists have learned a great deal about the effects and adverse effects of risperidone. One of these is that, although considered an atypical neuroleptic, it has a greater tendency to produce extrapyramidal symptoms (EPS) compared with other atypical neuroleptics approved in children, such as aripiprazole, olanzapine, and quetiapine. This is due to risperidone’s greater affinity for blocking dopamine 2 (D2) receptors, and in this regard it resembles typical neuroleptics such as haloperidol.

Another effect of risperidone’s comparatively stronger D2 blocking ability has been its tendency to produce a higher elevation of prolactin compared with other atypical neuroleptics. Neuroleptics such as risperidone, as well as many other drugs such as amphetamines, and even recreationally used or abused drugs such as cannabis, have been reported to lower prolactin. Such reported propensity of risperidone to induce hyperprolactinemia has led to a proliferation of opinions, concerns, and controversies as well as malpractice and class action lawsuits. These concerns and disputes include risperidone’s tendency to produce hyperprolactinemia, questions of whether there is a relationship between hyperprolactinemia and gynecomastia, how problematic or useful a drug such as risperidone is, whether the FDA should rescind the approval of risperidone and have it withdrawn from the market, how to prevent and properly identify gynecomastia (especially drug-induced gynecomastia) earlier, and how to deal with the issue of gynecomastia in psychiatric patients, especially in children treated with risperidone and other neuroleptics.

REVIEW OF THE LITERATURE

The imbalance between estrogen and androgen in breast tissue is thought to be the mechanism that produces gynecomastia, but how this occurs in idiopathic or drug-induced gynecomastia is unclear. The hormonal imbalance in favor of estrogen is believed to trigger glandular and ductal hyperplasia, causing gynecomastia. There is evidence that obesity and high body mass index are associated not only with pseudogynecomastia, but with gynecomastia as well. Peripheral conversion of androgens to estrogen in adipose tissue is considered a possible mechanism in such cases. A family tendency for persistent pubertal gynecomastia has been reported.

In a series of patients ages 10 to 20 years treated with risperidone, 43% were diagnosed as having gynecomastia compared with 21% of controls; however, the criteria used to diagnose gynecomastia were not mentioned. In the same group, although hyperprolactinemia was present in 47% of patients treated with risperidone, gynecomastia was not significantly associated with hyperprolactinemia. One hypothesis has been that because risperidone often increases prolactin levels, prolactin action on the breast tissue may be the cause for gynecomastia; however, this hypothesis has not been proven. In an analysis of data involving prolactin levels and adverse events in patients treated with risperidone, there was no significant correlation between prolactin level and adverse effects in men, including the emergence of possible prolactin-related side effects such as gynecomastia, decreased libido, and erectile dysfunction.

As far back as 1972, it had been shown that, although elevated prolactin may be an associated finding in some patients with gynecomastia, there was no evidence that prolactin is etiologically related to the development of gynecomastia. This understanding has not changed since then, and no direct link between hyperprolactinemia and gynecomastia has been established. In spite of such a lack of established connection between hyperprolactinemia and gynecomastia, media reports and advertisements for legal action portray this hypothesis as established facts. There are indications that pharmacogenomic variability may account for some of the differences in occurrence of drug-induced hyperprolactinemia and gynecomastia.

Prolactin may interfere with the release of gonadotropin-releasing hormone, which in turn may suppress testosterone level in men. Such changes are hypothesized to induce gynecomastia in susceptible men, but there is wide individual variability in the prolactin level hypothesized to cause gonadal hypofunction. Also, “Little is known about the clinical consequences of a sustained high prolactin level over years in children and adolescents.” The vast majority of men with elevated prolactin levels do not develop gynecomastia, and the majority of patients with gynecomastia have normal prolactin levels. However, this does not mean that elevated prolactin levels should be ignored. The possible but unproven association between neuroleptic-induced hyperprolactinemia and conditions such as higher rates of pituitary adenoma and reduction in bone mineral density, apart from the question of gynecomastia, makes it imperative that physicians exercise vigilance regarding the issue of hyperprolactinemia.

DIFFERENTIATING PSEUDOGYNECOMASTIA FROM TRUE GYNECOMASTIA

In true gynecomastia, on palpation of the breast, a palpable “firm disc of freely movable mass of glandular breast tissue under the areola of the nipple” is present, whereas in pseudogynecomastia, only the soft swelling of accumulation of fat is felt. However, this distinction may not be easy to make and it may not be conclusive, so there is a need for improvement in criteria and parameters for objective differentiation between the two conditions.
STEPs TO BE TAKEN BEFORE PRESCRIBING NEUROLEPTICS, INCLUDING RISPERIDONE, FOR CHILDREN

There is little doubt that prescribing neuroleptics for children should be undertaken with all the precautions necessary to avoid short-term and long-term adverse effects. These include being aware of the rare possibility of development of gynecomastia as an adverse effect of such medicines.

The first and foremost step that a child psychiatrist or prescriber needs to take in this context is to get fully informed consent from the parent before any medicine, including risperidone, is prescribed for a minor. Until now, informed consent was obtained mainly for neurolept-induced weight gain, metabolic syndrome, EPS, and potential for tardive dyskinesia. In today’s context, it is essential that psychiatrists prescribing neuroleptics specifically inform the parent (and child also, if deemed appropriate) as to gynecomastia being a rare but possible adverse effect and explain what gynecomastia is and the need to be aware of such a possibility. This will alert the parent and child to be aware of this potential problem and to report any breast-related problem. It is prudent to remember that drug-induced gynecomastia detected early is a much more reversible condition than if it goes undetected for 1 year or longer.6,8,10

Before risperidone or any other neuroleptic is prescribed, a recent physical examination from the child’s pediatrician should be obtained, and thereafter examinations should be performed at least once every 6 months to make sure the child remains in good physical health and free of adverse effects such as gynecomastia.

MANAGEMENT OF A CHILD SUSPECTED TO HAVE DEVELOPED GYNECOMASTIA RESULTING FROM NEUROLEPTIC TREATMENT

There are no clear directives or reliable studies in the literature as to the steps a child psychiatrist or any other physician should take when a child being treated with a neuroleptic is found to have gynecomastia.5,8,12,13

The suspicion or finding of gynecomastia may be incidental—usually detected by the pediatrician during a physical examination.7,8,10 Occasionally, it may be the psychiatrist’s own suspicion that brings the problem to focus. Gynecomastia in its early stages may produce pain in the subareolar region due to enlargement of breast tissue and may be the first symptom that alerts the physician to the possibility.7,8,10

Today, as a result of media publicity and television advertisements for class action lawsuits, increasing numbers of parents, teens, adults, and mental health professionals have been asking questions about the issue of gynecomastia and risperidone use.

Once the suspicion of gynecomastia occurs, the first step is to confirm by physical examination and observation.6,7,8,10

EXAMINATION OF THE MALE BREAST TO DETECT GYNECOMASTIA

Whether the child psychiatrist involved will do this preliminary observation and/or palpation of the breast, or whether the child will be referred to the pediatrician or another specialist without the psychiatrist making any personal observations, will depend on the confidence and comfort level of the psychiatrist in conducting such examination. In today’s litigious environment, it will be helpful for psychiatrists to develop the capacity to conduct a preliminary observation and palpation of the male breast to address the issue of possible gynecomastia. In Europe, some of the research studies on possible neuroleptic-induced gynecomastia were done by psychiatrists who obtained brief training and then conducted the examinations themselves.13 Such examination will inform the psychiatrist if the presence of gynecomastia is likely and, if so, what the approximate dimensions of the breast tissue enlargement are, whether there is very little likelihood of gynecomastia or whether the findings appear equivocal. It is also wise to remember that at times gynecomastia could be due to a serious pathology unrelated to puberty or drug treatment, and identifying such a problem early could lead to the best outcome.6,7,8,10

Observation and Palpation of the Male Breast for Gynecomastia

If the prescribing psychiatrist decides to undertake palpation of the child’s breast, then they must first and foremost explain to the parent and the child why such an examination is advisable and, once permission is granted, in the presence of the parent, visually examine the breast for any obvious enlargement and the approximate size of any enlargement, and record the findings. Before the breast area is palpated, the examiner should thoroughly wash his or her hands and put on examining gloves. They should first palpate the breast area with the flat of the hand to determine if any firm mass is felt under the areola or whether any swelling that may be visible is more likely due to accumulation of fat and, in that case, indicative of pseudogynecomastia.8,10 This should be followed by placing the thumb and forefinger, or two forefingers, on either side of the breast, with each finger placed about 2 inches away from the nipple, and slowly bringing the fingers together along the nipple level, feeling for the edges of any firm mass.8,10 If gynecomastia is present, the fingers will encounter the firm margins of the discoid enlargement of the breast tissue as a “freely movable mass, whose consistency is distinctly different” from that of the surrounding fat.8,10

In some cases, even experienced examiners may not be able to make a definite determination as to whether there is true gynecomastia or not,18 but in most cases, at least a preliminary determination of the presence or absence of gynecomastia can be made with reasonable certainty. The psychiatrist should record the findings and inform the parent and child of the find-
ings in a supportive manner and realistically reassure them and refer the child to the pediatrician or pediatric endocrinologist for a more detailed examination and any other investigations that may be appropriate. Even if the psychiatrist feels or decides he or she is not competent enough to conduct such observations or examination, or such examination is inconsistent with their style of practice, he or she can discuss concerns with the parent and child and allay their anxiety by educating them about gynecomastia in children. This should include giving information that physiological gynecomastia is common during pubertal years, that most often it is a benign and self-limiting condition, and that many drugs, including neuroleptics such as risperidone, can induce gynecomastia in a susceptible child, but in most cases stopping the offending drug will be enough for the swelling to diminish and disappear. 6,7,8,10

When referring the child to a specialist and collaborating in treatment, it is important to keep in mind that clinical evaluation must address diagnostic confirmation, search for an etiological factor, and classify gynecomastia into severity grades to guide treatment. 10 Gynecomastia can occur as a “slight protrusion limited to the areolar region” to a “Major breast hypertrophy…nipple-areolar complex positioned more than 1 cm below the inframammary fold,”10 and treatment may vary from “weight loss, reassurance, pharmacotherapy with tamoxifen, and surgical correction.”10

GYNECOMASTIA AND HYPERPROLACTINEMIA

Although many patients taking neuroleptics develop hyperprolactinemia, the vast majority do not develop gynecomastia as a result. However, unusually elevated prolactin levels in children treated with neuroleptics cannot be ignored. Some clinicians recommend that a child receiving risperidone or another neuroleptic should be considered for a switch to a drug that produces less elevation of prolactin if significant hyperprolactinemia develops, but there is no reliable study or guidance as to what level of asymptomatic hyperprolactinemia may be significant and indicates such a switch. 6,8,12,14 At present, the decision is based more on the comfort level of the prescribing physician regarding the issue than on a well thought out decision-making process. A switch from risperidone to aripiprazole, or addition of aripiprazole to risperidone, are the measures often recommended. 19,20 Although no correlation has been established between increase in prolactin level or the degree of prolactin elevation and the incidence of gynecomastia, in a child who is exhibiting prolactin elevation to an unusual degree, such a switch to a less prolactin-elevating drug is a wise and ethical action, as protecting the patient from any possible adverse effect, even a very remote or unproven one, is in keeping with good clinical and ethical practice. At present, the options for such a switch in children are aripiprazole, quetiapine, and olanzapine. The issue of when it is prudent to make such a switch and what are the possible risks and benefits in doing so remains an open question and deserves an informed approach that starts with the issue of monitoring prolactin level.

IS THERE A NEED TO MONITOR PROLACTIN LEVEL IN CHILDREN RECEIVING RISPERIDONE OR OTHER NEUROLEPTICS?

It is prudent to monitor prolactin level in children and adults who are prescribed risperidone and other neuroleptics known to increase prolactin level. At the very least, it will alert the clinician to unusually high and persistent prolactin levels, which may indicate unusual pharmacogenomic sensitivity to the D2 blocking action of the drug. 13 This should prompt the clinician to observe for any other unusual sensitivities, such as the rare occurrence of gynecomastia. Based on the usual time course of prolactin elevation induced by neuroleptics, 13 a measurement at baseline followed by quarterly measurements in the first year and half-yearly measurements thereafter appears prudent.

There are more studies regarding the increase in prolactin level and its possible relation to risperidone than any other neuroleptic. 13 Many studies have used a normal upper limit of 15 ng/mL of prolactin for adolescents, 14 although some studies have used levels as high as 15 to 25 ng/mL for men. 14 A comprehensive meta-analysis of studies involving risperidone use and hyperprolactinemia in children and adolescents revealed that, on average, risperidone increased prolactin level from 7.8 ng/mL to 17.7 ng/mL after 1 year of treatment and from 7.4 ng/mL to 24.9 ng/mL after 2 years of treatment. 13 The authors opined that prolactin levels may be influenced by “genetic differences that influence prolactin metabolism and D2 receptor density.” 13

ASYMPTOMATIC HYPERPROLACTINEMIA AND SWITCHING FROM RISPERIDONE TO ANOTHER NEUROLEPTIC TO PREVENT POSSIBLE ADVERSE EFFECTS

A switch from risperidone to another atypical neuroleptic does not mean the propensity to develop gynecomastia will be fully eliminated. Some studies have shown that although olanzapine produces less prolactin elevation than risperidone, at times it was associated with a higher incidence of gynecomastia. 13,14 Because aripiprazole has a very low tendency to produce hyperprolactinemia, it is usually the first choice for switching to as long as the child maintains improvement in clinical symptoms after the switch. Even addition of aripiprazole to risperidone has been reported to decrease prolactin level in an impressive manner. 19,20 Because the degree of risperidone-induced hyperprolactinemia has been found to be dose related, reduction of risperidone dose and addition of small doses of aripiprazole may be one
option. These measures may have application in situations where a child’s psychiatric problems may have shown robust response to risperidone, and discontinuing risperidone could not be achieved because of worsening symptomatology or poor response to alternative medicines has already occurred. In this author’s opinion, because there is little reliable research that gives guidance as to the level of hyperprolactinemia at which a switch from risperidone has to be seriously considered, and given that the usual increase in risperidone-induced prolactin level in boys and young men is to a level of 17 to 25 ng/mL, then any patients whose prolactin level is higher than 25 ng/mL should be closely monitored for adverse effects and a switch to another neuroleptic should be considered if the level goes above 50 ng/mL. The parent and/or patient should be informed of the findings and measures that can minimize the possibility of adverse effects in a manner appropriate for each individual.

**WHAT IF GYNECOMASTIA IS DETECTED IN A CHILD RECEIVING RISPERIDONE?**

If examination strongly indicates or proves that gynecomastia has developed, and the problem appears to be drug induced or may have a drug-induced component, the following steps may be prudent:

1. Discuss the options (listed below in steps 2 to 5) with the parent (and child when appropriate), including possible benefits and risks (steps 3 to 5) with the changes suggested and consider the steps below:
2. Continue collaboration with the specialist who has confirmed the diagnosis of gynecomastia.

3. Stop risperidone and observe the child without any neuroleptic, or on a non-neuroleptic medicine if that is feasible, taking into consideration that the illness for which the child is being treated may worsen. If the illness worsens be prepared to start treatment with an alternative neuroleptic such as aripiprazole, quetiapine, or olanzapine.

4. Immediately switch to aripiprazole or one of the other neuroleptics mentioned if the child’s psychiatric state makes it impossible to avoid treatment with a neuroleptic. At the time of this writing, quickly switching to aripiprazole may pose challenges because many insurance companies require preauthorization for aripiprazole and may even reject such requests.

5. If the child has already done poorly on the alternate medicines mentioned and gynecomastia is minimal or seems to have a strong pubertal component to it, attempting to maintain stability with a significantly lower dose of risperidone (with or without small dose of aripiprazole added) may be another option in children for whom treatment with risperidone has proven to be essential. In this case, make sure the rationale for such an action has been explained to the child’s parent and pediatrician and that all are in agreement for such a trial, and make sure the child will be closely monitored by all concerned to ensure that the gynecomastia is not worsening.

**ADDITIONAL STEPS IN THE DIAGNOSIS AND TREATMENT OF GYNECOMASTIA**

Most instances of drug-induced gynecomastia will diminish and disappear once the offending drug is withdrawn, and if discovered early enough the improvement may start appearing within a month or so. For a definitive diagnosis of gynecomastia, when clinical findings are equivocal or in other contentious situations, imaging measures such as sonography or mammography may become necessary. In very unusual situations, such as when plastic surgery is contemplated or when malpractice or other claims are being made, aspiration or other biopsy may be needed to prove or disprove that there is definite abnormal proliferation of breast tissue (the essential feature of true gynecomastia) and, if there is such proliferation, what are the dimensions and the grade.

If stopping the offending drug does not produce sufficient improvement in gynecomastia, treatment by a specialist with medicines such as tamoxifen is an option. The psychiatrist prescribing risperidone or any neuroleptic for children or adults needs to stay vigilant to the issue of drug-induced gynecomastia to avoid clinical, ethical, and legal pitfalls, as drug-induced gynecomastia has the best chance of reversal if detected early, as fibrotic changes take place later on in the breast tissue, making it less responsive to nonsurgical interventions.

**WHY PRESCRIBE RISPERIDONE AT ALL?**

In the past two decades, risperidone has been one of the most widely prescribed neuroleptics in children and adults, and there is a great deal of information, based on both research and clinical experience, regarding its usefulness and adverse effects. Recent studies involving large groups of adults have shown risperidone to be one of the most efficacious of all medicines approved for the treatment of schizophrenia and mania. In the same study, quetiapine and aripiprazole were shown to be less efficacious than risperidone, and olanzapine was worse in weight gain. Risperidone has also been found to be more effective than lithium and divalproex in the manic and mixed phases of bipolar disorder in children and adolescents, and of significant benefit to seriously disturbed children who fail to respond to psychosocial interventions. It has also been found to be significantly more beneficial to the more aggressive and disruptive of children with bipolar disorder compared with divalproex. Although risperidone may produce more EPS and hyperprolactinemia than some other atypical neuroleptics approved in children, with regard to other adverse effects such as sedation, postural hypotension, weight gain, and metabolic syndrome, it has a more favorable profile compared to other neu-
roleptics while maintaining a high level of efficacy. Less intense side effects such as drowsiness and postural hypotension means it allows children to function more optimally, especially in the school environment.

Compared with adults who are seriously mentally ill and receiving neuroleptics (most of whom may be receiving disability benefits and who probably do not have to work to earn a living), children who suffer from serious mental illness are expected to function and achieve in school like other children—a fact probably not fully appreciated by communities not affected. Moreover, a child who is doing well on risperidone may not necessarily do well on another neuroleptic, as clinical experience and some studies indicate. Switching from risperidone to another neuroleptic for an inadequate reason may prove unwise. Many children may have been prescribed risperidone after having failed to improve sufficiently on other neuroleptics or who did not tolerate them well enough to continue. In addition, risperidone has a unique FDA approval for autism-related irritability that most alternative neuroleptics do not have.

Some of the criticisms against risperidone appear to be based on the erroneous belief or misinterpretation that, because it raises prolactin level, it will automatically cause gynecomastia. This notion ignores the fact that the gynecomastia may be normally occurring pubertal gynecomastia or pseudogynecomastia caused by weight gain, which can occur with all neuroleptics.

Haloperidol, which has been found to have equal or greater tendency to cause hyperprolactinemia, gynecomastia, and extrapyramidal symptoms compared with risperidone, is still widely prescribed in the United States and other parts of the world for patients of all ages more than 40 years after its introduction in the market. There is greater experience with risperidone in children and adolescents and more carefully conducted research on the effectiveness and tolerability of risperidone than other typical and atypical neuroleptics.

Considering such facts, withdrawing the FDA approval for risperidone and removing it from the market as some have demanded will limit the treatment options for children and adults and expose many children with serious mentally illness, their parents, and other caregivers to more challenges with care.

Until better alternatives with equal or better effectiveness and fewer side effects become a reality, judicious use of risperidone needs to continue as an option for children and adults. The need for all psychiatrists and other prescribers, especially those who treat seriously ill children, to become more knowledgeable and vigilant about the issues discussed here is now more urgent than ever.

REFERENCES


