BEST PRACTICE RECOMMENDATIONS: USE OF ANTIDEPRESSANTS IN PREGNANCY AND LACTATION

by

Jeanne Camille Beauchamp

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A Master’s Report Submitted to the Faculty of the

COLLEGE OF NURSING

In Partial Fulfillment of the Requirements For the Degree of

MASTER OF SCIENCE IN NURSING

In the Graduate College

THE UNIVERSITY OF ARIZONA

2008
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ACKNOWLEDGMENTS

Thanks to Dr. Judith Berg and Gloanna Peek for all the time and energy spent in guidance for this project. This has truly been an educational and spiritual journey for me.
TABLE OF CONTENTS

LIST OF TABLES .................................................................................................................5

ABSTRACT.................................................................................................................................6

1. CHAPTER ONE ......................................................................................................................7
Introduction .................................................................................................................................7
Problem Statement ......................................................................................................................8
Statement of Purpose ...............................................................................................................10
Background and Definitions .................................................................................................10
Significance .............................................................................................................................13
  Summary .................................................................................................................................14

2. CHAPTER TWO ....................................................................................................................16
Theoretical Framework/Literature Review ............................................................................16
  Introduction ..........................................................................................................................16
  Overview of King’s Theory of Goal Attainment .................................................................16
  Project Detail .......................................................................................................................20
  Review of Literature .........................................................................................................23
  Summary ...............................................................................................................................34

3. CHAPTER THREE .................................................................................................................37
Introduction .............................................................................................................................37
Evaluation of King’s Theory of Goal Attainment for Project ...............................................37
  Strengths of Project ............................................................................................................38
  Limitations of Project .........................................................................................................39
  Significance ........................................................................................................................41
  Conclusions ........................................................................................................................43

TABLE 1 ..................................................................................................................................47
TABLE 2 ..................................................................................................................................48
TABLE 3 ..................................................................................................................................49

REFERENCES ..........................................................................................................................50
LIST OF TABLES

TABLE 1: Common Antidepressants.................................................................................47
TABLE 2: FDA Pregnancy Risk Categories........................................................................48
TABLE 3: Twenty-one Competencies for the Twenty-First Century........................................49
ABSTRACT

The purpose of this report was to examine the state of the science regarding the safety of the use of antidepressants during pregnancy and lactation. More specifically, to examine which antidepressants are safe for use during pregnancy, which are safe during lactation, and if there are differences between the medications that are safe during pregnancy versus lactation. King’s Theory of Goal Attainment provided a theoretical framework for this report. While conclusive data are still lacking, research has demonstrated that some antidepressants, most commonly SSRIs, are relatively safe for use during pregnancy and/or lactation.
CHAPTER 1

Introduction

The World Health Organization (WHO) includes mental health as a core part of its overall definition of health, “a state of complete physical, mental and social well-being, and not merely the absence of disease” (World Health Organization [WHO], 2007, Mental Health page). This inclusion of mental health as a key component of an overall wellness spectrum is echoed by the United States Department of Health and Human Services’ Healthy People 2010 initiative, which lists mental health as one of its ten leading health indicators (United States Department of Health and Human Services [USDHHS]a, 2007).

Within the realm of mental health exist a plethora of opportunities for inquiry. Indeed, enough knowledge and specialty are included in the mental health field that primary care providers such as family nurse practitioners face a challenge in remaining abreast of current research and practice guidelines. However, despite this challenge, it is incumbent on care providers to continually seek the highest available quality of information related to the safety and efficacy of treatment options. It is with this in mind that the author has ventured to compile information
regarding the use of antidepressants during pregnancy and lactation.

Problem Statement

Major depression is the most common psychiatric disorder that is likely to be encountered by the general practitioner, is approximately twice as common in women as it is in men, and is most likely to occur between the ages of 18-44 (Faulkner & Lipsky, 2005; Mian, 2005). This age interval coincides directly with the time of life during which most women bear their children, and also represents an age group that is likely to constitute a considerable proportion of the family nurse practitioner’s client population, depending on the care setting. Also, postpartum depression affects approximately 10-15% of women, and risk of postpartum depression is higher in women who have a history of major depression (Mian, 2005). Thusly, the general practitioner needs to be aware of the potential risks and resulting treatment implications that are relevant to a diagnosis of major depression during the intrapartum and postpartum periods.

Beyond the challenge of successfully identifying women who are suffering from major depression during pregnancy or postpartum, the nurse practitioner faces a series of
complex considerations when he or she treats a woman for major depression during pregnancy or postpartum. While evidence is growing to support the use of non-pharmacological methods such as phototherapy, negative ion generators, and psychotherapy as aids in the management of major depression (Faulkner & Lipsky, 2005; Hartwell-Walker, 2006; Mann, 2002), antidepressant medications remain a valuable treatment option, and an important consideration for the care provider and the client. In the case of a pregnancy, or in a depressed mother who wishes to breastfeed, the choice of the most appropriate therapy is not always clearly defined.

In large part due to the ethical concerns surrounding the administration of potentially toxic medication to pregnant women and infants and the potential risk of harm, conclusive data regarding the safety of antidepressants for use during pregnancy and/or lactation have been lacking (Altshuler et al., 2001). Whereas data from large scale, randomized and placebo-controlled trials are widely available to help generate guidelines and to inform decision-making regarding medication use in other health care settings for treatment of a variety of disorders, there have been comparatively few studies that have the
sample size, diversity, and systematic approach needed in order to offer sufficient statistical power and reliability to generate empirical data concerning antidepressant use during pregnancy and lactation (Altshuler et al., 2001).

Statement of Purpose

This report will focus on the best practice recommendations for the use of antidepressants during pregnancy and lactation. Its purpose will be to make useful commentary on current literature and research, and to compile information to answer the following questions:

1. Which antidepressants are safe during pregnancy?
2. Which antidepressants are safe during lactation?
3. What are the differences, if any, in the antidepressants that should be used during pregnancy versus during lactation?

Background and Definitions

Major depression refers to a mood disorder that is characterized by five or more of the following symptoms, which must have been present for at least two weeks: depressed mood; loss of interest or pleasure in daily activities; weight gain or loss; insomnia or hypersomnia; psychomotor agitation or retardation; fatigue or loss of energy; feelings of guilt or worthlessness; inability to
concentrate; and thoughts of death or suicidal ideation (Faulkner & Lipsky, 2005). Depression that occurs during pregnancy is sometimes referred to as perinatal depression, and postpartum depression is depression diagnosed within two weeks to one year following delivery (USDHHS b, 2007).

Depression is caused by an interaction between biological factors that predispose the individual to depressive illness with psychosocial and/or physiological stressors. However, our understanding of how exactly this interaction occurs is not complete. The prevailing wisdom suggests that there is some dysregulation of the neurotransmitters in the limbic-hypothalamic system, which is evidenced by symptoms of depressive illness as described above (Faulkner & Lipsky, 2005). These neurotransmitters include serotonin, norepinephrine, dopamine, and γ-aminobutyric acid (GABA), which form the targets for various antidepressant medications.

Depression, including postpartum depression, has typically been treated in the primary care setting with antidepressant medication, psychotherapy, or a combination of both. "The combination of antidepressant medications with psychotherapy has proven to demonstrate the best outcomes in treatment of depression" (Faulkner & Lipsky,
There are several types of antidepressant medications that are used to treat major depression: tricyclic antidepressants (TCAs) such as amitriptyline or nortriptyline; heterocyclics such as bupropion; selective serotonin re-uptake inhibitors (SSRIs) including fluoxetine, paroxetine, and sertraline; serotonin-norepinephrine re-uptake inhibitors (SNRIs) such as venlafaxine or duloxetine; monoamine oxidase inhibitors (MAOIs) including tranylcypromine and phenelzine; and “other” antidepressants including mirtazapine, trazodone, and nefazodone (Epocrates, 2008). There is no one medication that works equally well for all patients, and some cases require pharmacotherapy with more than one agent. Also, most medications have a dosage range instead of a fixed dose, and so the medications need to be titrated to the individual patient (see Table 1).

This consideration of treatment options becomes much more complex with the introduction of pregnancy and/or lactation to the equation. Although the combination of antidepressant medications and psychotherapy is the most effective regimen for treating major depression, the issue is complicated by concerns regarding maternal and fetal health and wellness outcomes. While research has made it
clear that untreated maternal depression places the fetus/infant at risk as well as placing the mother at risk, there are risks associated with the use of various medications during pregnancy and lactation that need to be balanced with concern for mother and infant health and safety. Risks to the fetus/infant include preterm delivery, lower Apgar scores, low birth weight, admission to neonatal special care units, birth complications, and fetal death. Maternal risks include spontaneous abortion, gestational hypertension, preeclampsia, and suicide attempts, (Bonari, et al., 2004; Haller, 2005; Wadhwa, Dunkel-Schetter, Chicz-DeMet, Porto, and Sandman, 1996). Risks of antidepressant medication exposure in utero are reported to include fetal anomalies and deformities, spontaneous abortion, fetal and neonatal death, neonatal withdrawal symptoms, and neurodevelopmental delays (Fereirra et al., 2007; Koren, 2004; Malm, Klaukka, & Neuvonen, 2005).

Significance
Perinatal and postpartum depression represent some of the most common psychiatric illnesses seen in the primary care setting. The effects of untreated depression can be deleterious to mother and infant, and the consequences of depressive illness can impact bonding behavior and family
dynamics (Bonari et al., 2004). Health care providers caring for pregnant and postpartum women have a unique opportunity to assess potential depressive symptoms, and have an obligation to provide the highest standard of care available based on current evidence. Concern for infant safety related to drug exposure in utero or via breastmilk should be balanced with risk factors related to untreated maternal depression as mentioned above. This report contributes to the competent care of women with perinatal and/or postpartum depression and their infants by collecting and synthesizing data relevant to the use of antidepressant medications during pregnancy and lactation.

Summary

Each person is a unique individual, whose illness and wellness are formed by an interaction between many elements. Mental health is a central element in the overall definition of health, and it provides innumerable opportunities for scholarly inquiry. This depth and breadth of field poses a challenge to the providers who care for patients in the primary care setting, as there is a large variety of potential treatments and responses to treatment.

Perinatal and postpartum depression are common psychiatric disorders, and there are a variety of
approaches to managing them. Many treatment options involve the use or consideration of use of psychopharmacology, which necessitates the consideration of possible adverse effects on the fetus and infant secondary to drug exposure \textit{in utero} or via breastmilk. There are several types of antidepressant medications, and several drugs within each type from which to choose. This report will investigate the safety of antidepressant use during pregnancy and lactation, and will explore potential differences in antidepressant medication selection for pregnancy versus lactation.
CHAPTER TWO

Theoretical Framework/Literature Review

Introduction

The purpose of this report was to explore the indications for the use of antidepressants during pregnancy and lactation, and to explore potential differences in the drugs of choice in pregnancy versus lactation. King’s Theory of Goal Attainment provides a theoretical framework for the review of literature. This chapter will present an overview of the Theory of Goal Attainment and will review current literature and research on the topic of antidepressant use during pregnancy and lactation.

Overview of King’s Theory of Goal Attainment

King’s Theory of Goal Attainment originated “at a time when nurses were striving to become professional practitioners and scientists” (Fawcett, 2001, pg. 311). At the time that King was developing the Theory of Goal Attainment, there was a notable lack of a body of knowledge specific to nursing, defined nursing theories, and terminology to qualify the nursing act and the nurse-patient relationship. The Theory of Goal Attainment was developed to help generate further knowledge in nursing as well as a concrete method of application for the nursing
process at large. King’s Theory of Goal Attainment is identified as a grand nursing theory (Willis, 2007). King herself, however, refers to it as a middle-range theory, “achievement of goals represents an outcome, and outcomes demonstrate evidence-based nursing practice. This is what makes my theory a middle-range theory” (King, 1999, pg. 293). So agrees Messmer (2006), “The critical variable in this process is mutual goal-setting, which makes the transaction process a middle-range theory” (pg. 227). Either perspective is arguable, although King differentiates between her Theory of Goal Attainment and her conceptual framework published in 1971, from which she derived the elements of Goal Attainment. It is then logical to view her larger conceptual framework as the grand theory, and the Theory of Goal Attainment as a middle-range theory.

King intended the Theory of Goal Attainment to be “used by nurses in any environment where nursing is practiced” (King, 1999, pg. 293), which is clearly inclusive of most primary care practice settings. The Theory of Goal Attainment is implemented in a variety of service settings (Frey, et al., 2002).
The Theory of Goal Attainment includes the Nursing Metaparadigm concepts of nursing, health, individuals, and environment among its concepts (Willis, 2007). Central concepts of the Theory of Goal Attainment are self, perception, roles, communication, interaction, transaction, growth and development, time, space, and stress (King, 1981). King’s TGA includes three hierarchical, interacting systems as the background within which the nurse-client dyad, which forms the basis of her model, are operating.

The three interacting systems are individuals, or personal systems; groups, or interpersonal systems, and society, or social systems. “Three distinct levels of operation exist: (1) the individual (2) the group, and (3) the society. These levels of analysis are conceived to be dynamic interacting systems... the unit of analysis in this configuration is human behavior” (King, 1971, pg. 21).

The three systems are the backdrop for the transaction process, which is the hallmark of her theory. The crux of this theory is the idea that nurses and their clients are involved in a mutual relationship, where each person’s perceptions of the other, their environment, and the situation result in judgments, which contribute to mutually agreed-upon goals. These goals, when achieved, constitute
goal attainment. “When the nurse and patient have established mutual understanding of events, mutually set goals to be achieved by the patient and agree on the means to achieve the goal, a transaction occurs” (King, 1971, pg. 90-91).

King proposes her transactions as the means by which to perform quality nursing care, “my more recent ideas are centered on transactions. Transactions are viewed as a flow of information from the environment through coding, transformation, and processing of sensory, linguistic, and neurophysiological elements, resulting in decision making that leads to human actions” (King, 1997, pg. 20). This carries many implications, “using my transaction process in every nursing situation demonstrates that every human being is of equal worth” (King, 1999, pg. 295). Given the inherent worth of each person, and given each person’s right to self-determination, King’s TGA clarifies a means by which to honor the wide variety of human experiences and perceptions. “The domain of nursing assumes person-environment interactions. The domain focus is helping individuals, families, groups, and communities maintain health. This indicates that nursing is a goal-seeking system” (King, 1997, pg. 21).
The information in the review of literature will be presented with respect to King's transaction process, and how the available science may shape the perceptions, judgments, and actions of the nurse-provider and the client.

Project Detail

The goal of this project was to examine the state of the science regarding the use of antidepressants during pregnancy and lactation, and to consider how this information would contribute to providing quality care on an individual basis to each client as an integrated whole. This inquiry began with a review of common antidepressants used for the treatment of depression in non-pregnant, non-lactating patients as a starting point. These medications include all of the aforementioned antidepressants in the various classes of TCAs, SSRIs, SNRIs, MAOIs, heterocyclics, and "others". In a similar manner, background information about the diagnostic criteria for depression was obtained, as well as information about what would constitute postpartum depression (Faulkner & Lipsky, 2005; USDHHS b, 2007).

The search for information continued by seeking information about antidepressants in general, and their
common dosages. Then background data about diagnostic
criteria for depression and postpartum depression were
gathered. Next, the author reviewed texts on the subject of
general medication safety in pregnancy and/or lactation,
and then centered more specifically on information about
antidepressant use during pregnancy and lactation within
these texts. Subsequently, multiple databases were searched
for articles concerning AD use during pregnancy and/or
lactation, and articles were selected based on their
currency and their relevance to the topic. This pool of
articles was then divided into those that were relevant to
AD use during pregnancy, those relevant to AD use during
lactation, or both, and these articles were then segregated
by the class of AD to which they applied.

Once common dosage range as well as generic and trade
names had been reviewed based on data available from drug
information software, texts, and internet-based resources,
the next step was to gather information specific to the use
of ADs in pregnancy and lactation. There are several texts
available on drug safety during pregnancy and/or lactation.
The most useful texts this author found included Koren’s
(2007) text mentioned below, Hale’s Medications and
Mother’s Milk (2006), and Briggs, Freeman, & Yaffe’s Drugs
in Pregnancy and Lactation (7th ed.) (2005). Each of the aforementioned texts is organized in an alphabetical fashion listed by individual drugs, and the latter two texts provide information about the characteristics and findings of the various studies that contribute to the body of knowledge available for that particular medication.

Following the procurement of medication data from these texts, searches were performed that utilized the Medline and CINAHL databases via Ovid, as well as the ISI Web of Science. Keywords used were antidepressants, pregnancy, and lactation. Each keyword was searched separately, and then searches were combined. Some results matched only antidepressants + pregnancy or antidepressants + lactation. Results were limited to full text, English language, and publication within the last ten years. The publishing timeframe was then reduced to the last six years, and the Web of Science (WOS) was the most utilized search tool.

Approximately 129 articles were found in response to the WOS query related to antidepressant use during either pregnancy and/or lactation. This was further reduced to fewer than 100 articles with direct relevance to the goals of this report once the additional limitation of
publication after 1998 was added. This pool of articles was then subdivided into groups of those pertaining to pregnancy, those pertaining to lactation, or both. Each of these categories was then broken down further by the class of antidepressants as described above. This left approximately ten articles for each class of antidepressants except for SSRIs, the findings of which are summarized in the Review of Literature.

Review of Literature

This report will examine the available literature regarding antidepressants in several classes: TCAs (amitriptyline and nortriptyline), bupropion, SSRIs (fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, escitalopram), SNRIs (duloxetine, venlafaxine), MAOIs, and Other antidepressants (mirtazapine, trazodone, nefazodone). Tricyclic antidepressants (TCAs) work by blocking the re-uptake of the neurotransmitters norepinephrine and serotonin at the neuronal level, which increases the available concentrations of these neurotransmitters in the synapse. The TCAs also have an effect on histaminic receptors, which is responsible for their anticholinergic and sedative properties. Bupropion works by inhibiting the re-uptake of norepinephrine and
dopamine; its additional action as an antagonist of the nicotinic receptors is responsible for its application as an aid to smoking cessation. As their name implies, selective serotonin re-uptake inhibitors (SSRIs) target the re-uptake of the neurotransmitter serotonin in the synapse and thusly increase available concentrations of serotonin. Serotonin-norepinephrine re-uptake inhibitors (SNRIs) act to inhibit the re-uptake of both serotonin and norepinephrine in the synapse, but unlike TCAs, they do not have activity on histaminic receptors (Epocrates, 2008).

MAOIs treat depression by inhibiting monoamine oxidase, which is responsible for the breakdown of neurotransmitters including serotonin, dopamine, and norepinephrine. The inhibition of this breakdown increases the available concentrations of these neurotransmitters in the synapse. The class of “other” antidepressants includes drugs with different mechanisms of action. Mirtazapine works by blocking receptors that inhibit the secretion of norepinephrine and serotonin, which serves to increase the concentration of these neurotransmitters in the synapse. Trazodone’s exact mechanism of action is unknown, but it is believed to be due to inhibition of serotonin re-uptake. Nefazodone is similar to trazodone in that its exact
mechanism of action is unknown. However, unlike trazodone, nefazodone is believed to work by inhibiting both norepinephrine and serotonin re-uptake, as well as by inhibition of 5-HT2 receptors (Epocrates, 2008).

All medications are assigned a Pregnancy Risk Category by the U.S. Food and Drug Administration (FDA) based on the amount and quality of available data on a given drug. These FDA Pregnancy Risk Categories are summarized in Table 2 (pg. 57-58).

The work of Dr. Gideon Koren is prominent among current literature regarding the use of psychotropic medications in general, and antidepressants in particular, during pregnancy and lactation. His latest text, Medication Safety in Pregnancy & Breastfeeding: The Evidence-Based A-to-Z Clinician’s Guide, looks at each medication individually, and then considers some medications by class in later chapters. His analysis of each medication looks at risk/benefit during pregnancy, and risk/benefit during lactation for that drug.

Amitriptyline and nortriptyline, two common TCAs, are considered safe during pregnancy, as there is no apparent risk of malformations (Koren, 2007). A growing body of data echoes this finding regarding these two TCAs, although
others such as doxepin may have a less favorable profile for use in lactation (Eberhard-Gran, Eskild, & Opjordsmoen, 2006; Jain & Lacy, 2005; Koren, 2004; Nulman et al., 2002; Pearson et al., 2007). Potential exists for a poor neonatal adaptation/withdrawal-type syndrome when antidepressants are used in late pregnancy, a syndrome that is mentioned in a great deal of literature on antidepressant use during pregnancy. This syndrome is not unique to TCAs, and has been described with SSRIs, SNRIs, and heterocyclics (Ferreira et al., 2006; Kallen, 2007; Kalra, Einarson, & Koren, 2005; Koren, 2007). Koren (2004, 2005, 2007) mentions the neonatal withdrawal syndrome as an important consideration when using TCAs in late pregnancy.

This set of withdrawal-type symptoms includes jitteriness, hypertonicity, irritability, hypoglycemia, feeding difficulties, and respiratory distress (Pearson, et al., 2007). It has generally been found to be self-limiting, and available data suggest that there are no long-term neurobehavioral consequences for the affected individuals in terms of global intelligence quotient (IQ), language development, cognition, or temperament (Nulman et al., 2002). In terms of the TGA and the transaction model, this information may help to inform the provider and the
pregnant or breastfeeding patient about the viability of TCAs as a treatment option during pregnancy and/or lactation, with consideration for the potential need for increased monitoring of the infant after birth.

Amitriptyline and nortriptyline are excreted in breastmilk in very small amounts (Hale, 2006). Drug excretion into breastmilk is minor, and infant absorption is minimal, "an infant would consume approximately 21.5µg/kg/day, a dose that is unlikely to be clinically relevant. ...Both drugs were essentially undetectable in the infant’s serum" (Hale, 2006, pg. 51). While SSRIs are becoming more commonly favored for treatment of major depression during pregnancy and postpartum due to decreased incidence of anticholinergic side effects in the mother when compared with other classes of antidepressants, TCAs represent a reasonable choice once provider and client have mutually agreed upon the risk/benefit assessment (Eberhard-Gran, Eskild, & Opjordsmoen, 2006).

Bupropion carries no apparent risk of congenital malformations, and no apparent neonatal risk when breastfeeding (Cole et al., 2006; Hale, 2006; Jain & Lacy, 2005; Koren, 2007). Plasma levels studied in breastfeeding infants have ranged from undetectable to minimal, although
use of bupropion in a lactating mother is unadvisable if a seizure disorder is suspected in the neonate, as a known side effect of bupropion is a lowering of the seizure threshold (Hale, 2006). The decision to prescribe bupropion to a pregnant or lactating patient, or to continue with bupropion treatment during pregnancy and lactation, should take into account the available safety data as well as the woman and her family’s perceptions about her health and the potential risks to the fetus and infant.

SSRIs are the most widely studied class of antidepressants for use during pregnancy and lactation. Fluoxetine, paroxetine, and sertraline are common SSRIs and have been on the market considerably longer than some newer SSRIs including citalopram and escitalopram (Jain & Lacy, 2005). Fluvoxamine is chemically unrelated to other SSRIs, but produces similar effects. It is most often used for the treatment of obsessive-compulsive disorder, but is also an antidepressant. Multiple studies with very small sample sizes have shown minute or undetectable amounts of drug excreted in breastmilk, and multiple studies have found no increased risk of fetal malformation (Hale, 2006; Koren, 2007).
As a class, SSRIs have not been found to cause an increase in incidence of fetal malformations (Bellantuono, Migliarese, & Gentile, 2007; Hallberg and Sjoblom, 2005; Hale, 2006; Koren, 2007; Malm, Klauckka, & Neuvonen, 2005; Newport, Wilcox, & Stowe, 2001; Pearson et al., 2007). However, some studies have emerged regarding the use of paroxetine in early pregnancy and increased incidence of congenital cardiac malformation (Bar-Oz et al., 2007; Kallen and Olausson, 2006). Koren (2007) is critical of these studies and states, “At the present time, these data are based on non peer-reviewed studies. Therefore, one needs to be extremely careful in accepting them as scientific facts” (pg. 287). While it is clear that more investigation is required before a definitive judgment can be made, most references suggest caution with paroxetine use in early pregnancy.

There is also an FDA safety report regarding the use of SSRIs after the 20th week of gestation and incidence of persistent pulmonary hypertension of the newborn (Federal Drug Administration [FDA], 2006). This warning is based on one retrospective case-control report, and like the data regarding potentially increased risk of cardiac malformation with paroxetine, should be viewed as a
developing part of the larger body of knowledge related to antidepressant safety during pregnancy and lactation. Similar to other antidepressants in general, as well as SSRIs in particular, the decision to use or continue these medications in pregnancy needs to be based on a consideration of current knowledge of drug safety as well as the woman and her support network and their preferences based on the best information available.

Apart from the potential for fetal malformations, which is related to SSRI exposure in early pregnancy, there is well-documented risk for a neonatal withdrawal syndrome associated with SSRI exposure in late pregnancy. However, this syndrome or set of symptoms is also documented as self-limiting and lacking long-term effect on the health status of the infant, which would suggest that provider and patient awareness of potential risk would enable safe use of these drugs during late pregnancy if the mother’s condition had been appropriately assessed. (Ferreira et al., 2006; Hallberg and Sjoblom, 2005; Hale, 2006; Jain and Lacy, 2005; Kallen, 2007; Kalra, Einarson, and Koren, 2005; Koren, 2004; Koren, 2005; Koren, 2007; Malm, Klaukka, & Neuvonen, 2005; Pearson, et al., 2007). Some literature suggests that tapering the dose of SSRIs in the weeks
before delivery may be an acceptable strategy to minimize
the risk of neonatal withdrawal. This strategy needs to be
balanced with the risk of relapse of the depressive
illness, especially in a severely depressed mother

There are very few studies available on citalopram,
and currently no studies available on escitalopram for use
during pregnancy and lactation (Hale, 2006; Jain and Lacy,
2005). The studies on citalopram, each with a small sample
size, showed minimal passage of drug to breastmilk. There
are unpublished case reports and reports from manufacturers
suggesting a potential for increased somnolence in neonates
exposed to maternal citalopram via breastmilk, and so
cautions are advised and specific attention should be paid to
observing infant sleep behaviors (Hale, 2006; Koren, 2007).
Escitalopram is presumed to behave in identical fashion to
citalopram and so similar suggestions for caution apply,
although it is again acknowledged that there are currently
no data available (Hale, 2006).

Sertraline does not seem to be affected by the same
concern over cardiac malformations as paroxetine when used
during early pregnancy. Fluoxetine and citalopram produce
the most fetal medication exposure, while paroxetine and
sertraline produce undetectable drug levels in infants. In terms of lactation, this would suggest that paroxetine and sertraline would be more favorable SSRI choices if drug initiation were occurring during lactation (Jain and Lacy, 2005). When taking into account the perspectives that will inform care decisions, the long-term benefits of breastfeeding for the mother and infant as well as the potential risk of suboptimal outcomes due to untreated depression on maternal, infant, and family health should be reviewed.

SNRIs are a newer class of antidepressant than the SSRIs, and consequently there is less information available about their safety for use during pregnancy and lactation. Duloxetine is less well studied for these applications than venlafaxine, although it is presumed to be similar until proven otherwise (Hale, 2006). There have been some data that report an increased incidence of a more severe neonatal withdrawal syndrome with venlafaxine versus other SSRIs, but it has low excretion in breastmilk and is considered probably safe for use during lactation (Hale, 2006).

MAOIs have fewer safety data available than do SSRIs regarding risk for fetal malformation, and they carry a
much higher risk of adverse effects on the mother including multiple drug interactions and risk for hypertensive crisis. They also require specific and often troublesome dietary restrictions, and so based on this clinical picture, are considered essentially unacceptable for use during pregnancy unless maternal benefit clearly outweighs the potential risks (Hale, 2006; Jain and Lacy, 2005; Koren, 2007). There are no human data available for safety of MAOIs during breastfeeding (Hale, 2006; Koren, 2007).

The class of “other” antidepressants including mirtazapine, trazodone, and nefazodone is a varied group. Mirtazapine is unrelated to other antidepressants, and is considered pregnancy risk category C, which means that either animal studies show no adverse fetal effects and there are no controlled studies in women or that there are no data available (see Table 2). Studies which were limited by very small sample size showed very low mirtazapine concentrations in breastmilk and infant serum and no adverse effects on the infants, although lactation safety is still considered unknown by some resources (Epocrates, 2008; Hale, 2006).

Trazodone and nefazodone show no apparent risk of fetal malformation, although trazodone is more well-studied
than nefazodone (Hale, 2006; Koren, 2007). Trazodone is considered moderately safe for use during lactation, as it is excreted in very low quantities in breastmilk. There are some reports of infant drowsiness and lethargy in a breastfeeding neonate with maternal use of nefazodone (Hale, 2006). Both drugs are considered pregnancy category C, although nefazodone is considered possibly unsafe for lactation (Epocrates, 2008). As with the other classes of antidepressants discussed above, the decision about appropriateness and choice of drug therapy should involve a process of learning and discussion between the provider and the patient and family.

Summary

SSRIs are the most well studied class of antidepressants for use during pregnancy and lactation, and select TCAs also seem to have a favorable risk profile in some cases. While none of the antidepressants has been unconditionally labeled as safe for use during pregnancy and lactation, an overall picture of the client, the client’s family support network, and the severity of the depressive illness needs to inform the decision making and transaction process. For example, an expert panel reached an 83% consensus that severely depressed women who become
pregnant while on medication should continue their medication, possibly switching to a “safer” antidepressant if needed. While expert opinions varied on whether to treat milder depression with antidepressants or to try psychotherapy alone as a first line treatment, it is clear that in some cases, antidepressant use during pregnancy and/or lactation is warranted (Altshuler, et al., 2001).

King’s Theory of Goal Attainment provides a useful theoretical framework from within which to view choices about the most appropriate care for each individual client. This is in large part due to the subjective nature of the decision about what kind of psychopharmacological treatment to use during pregnancy and/or lactation, if any, and the variety of differences between each patient’s risk versus benefit assessment. By using a middle-range nursing theory to guide the inquiry, the author aimed to maximize the contribution of nursing theory to an advanced practice nursing care scenario while still balancing the need for scientific, research based data. For the purposes of this report, the Theory of Goal Attainment elucidated and encompassed the author’s view that nursing theory and interdisciplinary health science knowledge interact to shape each transaction between provider and client.
Current scientific knowledge helps to shape the perceptions of the nurse-provider, and this knowledge should be shared with the client in the context of informed decision-making. The judgments about what course of action will help to achieve the mutually agreed-upon goals related to treatment of depression during pregnancy and/or the postpartum period then inform the choice about how to direct treatment. The responses to the chosen treatment options help to assess the ongoing appropriateness of the selected method, and will aid in the selection of future courses of action.
CHAPTER THREE

Introduction

The aim of this inquiry was to investigate the best practice regarding antidepressant use during pregnancy and lactation. In contrast with other illness states across the lifespan, there is a relative paucity of high-quality data available to govern the formation of practice guidelines for the pharmacological treatment of perinatal or postpartum depression (Altshuler, et al., 2001). This renders the choice about how to best manage these conditions a complex challenge for care providers. As nursing in particular, and health care in general, strive towards evidence-based practice and evaluation of outcomes, it becomes increasingly important to investigate what constitutes best care.

Evaluation of King’s Theory of Goal Attainment for Project

Even when more structured guidelines do exist, the importance of considering each individual client’s health picture cannot be overstated. The Theory of Goal Attainment and its transaction process, by operating on the basis that each human is of equal worth and that evidence-based practice is the standard of care, create a structure that applies to every practice setting. By viewing the use of
antidepressants during pregnancy and lactation through the lens of the Theory of Goal Attainment, nurse-providers can remain engaged in the care process with their clients while continually striving to refine current understanding of the pharmacological management of perinatal and postpartum depression. This approach to the subject will help to enhance existing knowledge about the use of antidepressants during pregnancy and lactation in much the same way that King conceived of the Theory of Goal Attainment to help generate further nursing knowledge and theory (Frey, et al., 2002).

Strengths of Project

While not having well-defined guidelines on a subject can be concerning for providers and patients alike, it can also be an opportunity to contribute to an existing body of knowledge. An encouraging aspect about the use of antidepressants during pregnancy and lactation is the idea that there is ongoing inquiry into the subject, and there are more data emerging on an ongoing basis. The author attempted to elucidate what is known on this subject with this report, while also acknowledging what is not known. Ideally, this balance contributed to the strength of this project.
Maternal and child health will likely continue to be an important focus for the foreseeable future of health care, and the pharmacological treatment of perinatal and postpartum depression constitutes an important part of that picture. To that end, there is clearly potential to impact the lives and the health of many people, which represents one strength of this report. In addition, this report has potential to provide useful information to general practitioners, who are likely to deal with perinatal and/or postpartum depression in the course of their practice.

The goal of this report was help to clarify some of the common concerns that providers and patients may share regarding the use of antidepressants during pregnancy and lactation. In a more general sense, nurse-providers and their patients already share the common goal of good outcomes in terms of healthy pregnancies, healthy offspring, and healthy families. Developing more means by which to pursue that end is incumbent on the field of nursing and on health care in general, and the author has endeavored to participate in that venture with this report.

Limitations

Some limitations of this inquiry include a relative lack of high-quality evidence data as compared with other
issues relevant to health and illness. While an investigation into the most appropriate pharmacological management for a disorder such as diabetes mellitus or hyperlipidemia would very likely generate a large body of evidence from which to make educated decisions, pharmacological management of major depression during pregnancy and lactation is still in the development stage. While there are several medications that have been used during pregnancy and/or lactation for many years, much of the available literature examines this safety profile from a retrospective standpoint or with a limited sample size, which leaves very real possibilities of significant error and/or reduced generalizability. Therefore, an inquiry based on this body of literature would also be subject to that same concern.

An additional limitation of this project is its use of a middle-range nursing theory for its theoretical framework. While the author found King’s Theory of Goal Attainment to be the most appropriate for a body of knowledge that is still experiencing significant development, it is not as specific as short-range nursing theories that address a particular phenomenon or behavior. This lack of specificity may hinder the author’s goal of
informed commentary on the use of antidepressants during pregnancy and lactation, but it may also contribute to the depth of future investigations into the subject by this and other authors.

Because of its nursing focus, this report may not appeal to the practice of medicine by physicians, which is another of its limitations. While the goal of a collegial relationship between medicine and nursing is central to the competencies of advanced practice nursing, this goal is at times not fully actualized in daily practice (The Center for the Health Professions, 2008). The author’s concept of this report is that it incorporates most of the twenty-one competencies for the twenty-first century as described below (see Table 3). However, it is clear that more data are needed in order to establish comprehensive guidelines.

Significance

Given the relative lack of high-quality research data with which to formulate evidence-based guidelines, it is no small task to make intelligent commentary on what constitutes “best practice” for the use of antidepressants during pregnancy and lactation. However, it does seem clear that there are some relatively safe options for the pharmacological treatment of perinatal and postpartum
depression for mothers wishing to breastfeed. Each treatment option needs to be carefully considered within the context of each individual client’s preferences, values, and support network.

Beyond the scope of individualized patient care decisions, this report also has significance to the larger fold of health care and policy. While many other developed nations have national reporting systems for health care delivery, prescription medications, drug safety, and/or outcomes data, the United States lacks such an infrastructure. For example, Toronto’s Motherisk program has yielded a large amount of contributory information to modern literature about antidepressant use during pregnancy and lactation, and the United States could clearly benefit from establishment of similar programs (Hospital for Sick Children, 2007). Mental health is a key health indicator for large-scale efforts including Healthy People 2010 and the World Health Organization, and maternal and infant health are longstanding priorities (USDHHS(a), 2007; WHO, 2008). In the spirit of contributing to continuous improvement in the pharmacological treatment of MD during pregnancy and lactation, this paper advocates for policy that would create such programs.
Conclusions

Given the current state of the science regarding the use of antidepressants during pregnancy and lactation, the next step becomes a question of how this knowledge is implemented into nurse-provider practice. Prudent decision-making involves the perceptions of the provider and the patient, each operating within a larger context — the healthcare community for the provider, and the family and social community for the patient. These perceptions then lead to judgments, which lead to actions. Since there is very little about the treatment of major depression, irrespective of pregnancy and lactation, that is clear-cut, it stands the test of reason that the addition of pregnancy and/or breastfeeding to the equation might increase the depth of decision-making complexity.

How the current data will be used to shape the “best practice” needs to be examined for each specific patient case — there are no established guidelines for antidepressant use in pregnancy and lactation as there are for the use of antihypertensives or reduction of cholesterol. The healthcare community will hopefully be able to contribute to the establishment of such guidelines in the future as more data are gathered. Many other
developed nations have programs for reporting disease, drug registries, birth registries, and databases to collect and analyze outcomes of healthcare utilization, and in fact, several of the articles that provided useful information for this report came from other countries including Canada, Finland, the United Kingdom (UK), and Sweden. The United States lags noticeably behind these and, in fact, most other developed nations in terms of its maternal and infant mortality, and so a redirected focus on maternal and infant care and a more socialized approach to health may help to ameliorate this situation (Geography IQ, 2008; WHO, 2008).

As a prominent aspect of health in general, mental health care is a reasonable target for improvement efforts, and as previously mentioned, major depression represents the most common mental health disorder seen in general practice (Faulkner & Lipsky, 2005).

Armed with current knowledge that many antidepressants are considered somewhat safe to use during pregnancy and/or lactation, and that this safety profile needs to be balanced with client and family perceptions and wishes regarding care decisions, the nurse-provider faces a challenge about how to best support each patient. While it would be completely inappropriate to give false
reassurances about the complete safety of antidepressants for use during pregnancy and lactation, once a decision has been reached by the care team and the family about how to proceed, the nurse-provider should give reassurance that he or she will remain engaged in the process with the patient and family. This ongoing involvement allows for evaluation of outcomes, and ideally, would help to generate a larger, more comprehensive body of data that would be available to generate future guidelines regarding the use of antidepressants during pregnancy and lactation.

There is a remarkable variety of information resources available to health care providers and consumers alike, and the body of knowledge is growing. However, there are some areas that have not progressed as rapidly as others. While maternal and child safety are on the forefront of many health care agendas, our information about what constitutes “best practice” for depressed women who are pregnant or breastfeeding has not developed at the same pace as our knowledge about management of other illnesses, or even that of depression not occurring during pregnancy or lactation.

The goal of this project was to review the current literature about use of antidepressants during pregnancy and lactation, and to come abreast of the state of the
science. The means by which providers can implement safe and effective care for perinatal and/or postpartum depression is not yet definitively defined. However, by utilizing current information resources and ongoing dialogue in order to make care decisions, nurse-providers can give reassurance to their clients that they are receiving the highest standard of care. Remaining aware of and engaged in the transaction process helps to evaluate outcomes and will help to generate a deeper and broader body of knowledge.
## TABLE 1

**Common Antidepressants**

<table>
<thead>
<tr>
<th>MEDICATION NAME</th>
<th>MEDICATION CLASS</th>
<th>DOSAGE RANGE /DAY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>TCA</td>
<td>50-150mg</td>
</tr>
<tr>
<td>Bupropion</td>
<td>Heterocyclic</td>
<td>300-450mg</td>
</tr>
<tr>
<td>Citalopram</td>
<td>SSRI</td>
<td>20-60mg</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>SNRI</td>
<td>60-120mg</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>SSRI</td>
<td>10-20mg</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>SSRI</td>
<td>20-60mg</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>SSRI</td>
<td>100-300mg</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>Other</td>
<td>15-45mg</td>
</tr>
<tr>
<td>Nefazodone</td>
<td>Other</td>
<td>300-600mg</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>TCA</td>
<td>50-150mg</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>SSRI</td>
<td>20-50mg</td>
</tr>
<tr>
<td>Phenelzine</td>
<td>MAOI</td>
<td>45-90mg</td>
</tr>
<tr>
<td>Sertraline</td>
<td>SSRI</td>
<td>50-200mg</td>
</tr>
<tr>
<td>Tranylcypromine</td>
<td>MAOI</td>
<td>30-60mg</td>
</tr>
<tr>
<td>Trazodone</td>
<td>Other</td>
<td>100-400mg</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>SNRI</td>
<td>75-375mg</td>
</tr>
<tr>
<td>FDA PREGNANCY RISK CATEGORY</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>Controlled studies in women fail to demonstrate a risk to the fetus in the first trimester (and there is no evidence of a risk in later trimesters) and the possibility of fetal harm appears remote.</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>Either animal-reproduction studies have not demonstrated a fetal risk, but there are no controlled studies in pregnant women, or animal-reproduction have shown an adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester (and there is no evidence of a risk in later trimesters).</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>Either studies in animals have revealed adverse effects on the fetus (teratogenic, embryocidal, or other) and there are no controlled studies in women, or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).</td>
<td></td>
</tr>
<tr>
<td>X</td>
<td>Studies in animals or human beings have demonstrated fetal abnormalities, or there is evidence of fetal risk based on human experience, or both, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit. This drug is contraindicated in women who are or may become pregnant.</td>
<td></td>
</tr>
</tbody>
</table>
### TABLE 3

**Twenty-one Competencies for the Twenty-first Century**

<table>
<thead>
<tr>
<th>Competency</th>
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<tbody>
<tr>
<td>1. Embrace a personal ethic of social responsibility and service.</td>
</tr>
<tr>
<td>2. Exhibit ethical behavior in all professional activities.</td>
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<tr>
<td>3. Provide evidence-based, clinically competent care.</td>
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<tr>
<td>4. Incorporate the multiple determinants of health in clinical care.</td>
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<tr>
<td>5. Apply knowledge of the new sciences.</td>
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<tr>
<td>6. Demonstrate critical thinking, reflection, and problem-solving skills.</td>
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<tr>
<td>7. Understand the role of primary care.</td>
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<tr>
<td>9. Integrate population-based care and services into practice.</td>
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<tr>
<td>10. Improve access to health care for those with unmet needs.</td>
</tr>
<tr>
<td>11. Practice relationship-centered care with individuals and families.</td>
</tr>
<tr>
<td>12. Provide culturally sensitive care to a diverse society.</td>
</tr>
<tr>
<td>13. Partner with communities in health care decisions.</td>
</tr>
<tr>
<td>14. Use communication and information technology effectively and appropriately.</td>
</tr>
<tr>
<td>15. Work in interdisciplinary teams.</td>
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<tr>
<td>16. Ensure care that balances individual, professional, system, and societal needs.</td>
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<tr>
<td>17. Practice leadership.</td>
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<tr>
<td>18. Take responsibility for quality of care and health outcomes at all levels.</td>
</tr>
<tr>
<td>19. Contribute to continuous improvement of the health care system.</td>
</tr>
<tr>
<td>20. Advocate for public policy that promotes and protects the health of the public.</td>
</tr>
<tr>
<td>21. Continue to learn and help others learn.</td>
</tr>
</tbody>
</table>
References:


