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RISK v BENEFITS: THE USE OF SELECTIVE SEROTONIN REUPTAKE INHIBITORS IN CHILDREN

Kim Wilton*

INTRODUCTION

Selective Serotonin Reuptake Inhibitors (SSRIs) are a class of antidepressant medications that came on the market in the late eighties and early nineties. SSRIs were found to be clinically effective in treating clinical depression, and anxiety disorders in adults and had less cumbersome side effects compared to the older Tricyclic antidepressants.¹ The first drug in this class introduced was fluoxetine (Prozac), which was soon followed by paroxetine (Paxil), sertraline (Zoloft), citalopram (Celexa), fluvoxamine (Luvox), and escitalopram (Lexapro). Today the uses of SSRIs have broadened to include treatment for “Post-Traumatic Stress Disorder, pre-menstrual dysphoric disorder, urinary incontinence” and many other seemingly unrelated conditions.² In North America, “it is estimated that 2% of children and up to 8% of adolescents suffer from a depressive disorder. In addition, at least 10% of youth suffer from anxiety disorders.”³ Given the prevalence of childhood depression and anxiety disorders, it is not surprising that in the 1990’s and early 2000’s, SSRIs became the

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¹ Rebecca Ronsley et al, “Do Hospital and Community SSRI Usage Patterns in Children and Adolescents Match the Evidence?” (2010) 19:3 *Journal of the Canadian Academy of Child and Adolescent Psychiatry* 218.

² Trudo Lemmens & Ron A Bouchard, “Regulation of Pharmaceuticals in Canada” in Jocelyn Downie, Timothy Caulfield & Colleen M Flood eds, *Canadian Health Law and Policy* (Markham: LexisNexis, 2007) at 335.

³ Ronsley, *supra* note 1 at 218.

treatment of choice in fighting childhood depression and anxiety.⁴ Not only were SSRIs prescribed to adolescents and prepubescent children, they were commonly prescribed to kindergarten aged children and even infants less than a year old.⁵

However, SSRIs were not clinically tested for use in children and adolescents, nor were they approved for use in children and adolescents. SSRIs were prescribed to children and adolescents “off-label” by physicians, meaning SSRIs had not received approval for use in these age groups by Health Canada. In the first part of the 21st century, concerns began to arise concerning the use of these drugs in children and adolescents as reports began to emerge demonstrating that in many cases SSRIs were associated with an increase in suicidal behavior and thoughts in children and adolescents.⁶ Despite being subjected to regulatory warnings from Health Canada and intense media coverage, SSRIs are still widely prescribed to children and adolescents.

In this paper, I will review how SSRIs are currently regulated for use as a treatment for depression and anxiety in children and adolescents in Canada by examining the roles of the different actors involved, including: drug manufacturers, regulatory bodies, professional associations, physicians, parents and the patients themselves. In Part II of this paper I will discuss the 2004 warnings issued by regulatory agencies in Canada, the USA and the UK, against the use of SSRIs in children and adolescents; in Part III I will analyze the current off-label status of SSRIs for children and adolescents and the current system used by physicians to prescribe SSRIs to children and adolescents; and in Part IV I will discuss the problems that exist with the current system by examining the roles of each of the abovementioned actors. Finally, in Part V, I will make suggestions as to how the current system can be reformed and improved. The continued off-label use of SSRIs in children is not only dangerous for short-term use in children and adolescents, but could also have dangerous long-term effects as the consequences of SSRIs on child and adolescent development is unknown. The current regulatory system fails to protect this vulnerable population and exposes them to unwarranted and unnecessary risks. A new system is needed in which drug manufacturers are more accountable, regulatory warnings are more forceful, the ability of physicians to prescribe off-label is curtailed, and patients and their parents are more informed about treatment options.

⁴ The prescribing of a wide variety of psychotropic medication: Tricyclic Antidepressants, neuroleptic prescriptions, and ADHD medications, to children and adolescents has been increasing “dramatically” in the USA and Canada for the past several decades: see Audrey L. Zakriski, et al. “Justifiable Psychopharmacology or Overzealous prescription? Examining Parental Reports of Lifetime Pre-Prescription Histories of Psychiatrically Hospitalized Children” (2005) 10:1 Child and Adolescent Mental Health; Sharon Kirkey, “Psychiatry’s Bible: Book could roll out a whole new list of disorders and more prescriptions for psychoactive drugs” *Canwest News Service* (26 April 2010); Many physicians have criticized what they see as an “overzealous prescribing” of psychotropic medications in children and adolescents: Raymond Behr, “Overzealous Prescribing of Medications” (1998) 37:9 Journal of the American Academy of Child and Adolescent Psychiatry 900.

⁵ Jonathan Leo, “The SSRI Trials in Children: Disturbing Implications for Academic Medicine” (2006) 8:1 Ethical Human Psychology and Psychiatry 29 at 30.

⁶ *Ibid.*

I. THE 2004 WARNINGS: THE DARK SIDE OF SSRIs

Between 2003 and 2004, concerns arose about the safety and effectivity of SSRI use in children. Reports and meta-analyses of randomized controlled trials (RCTS) showed that SSRI use in children was correlated with increased risks of suicidal behavior and thoughts (also known as suicidality).⁷ Notably, the SSRI Paxil was found to create two times as much suicidal ideation in childhood, compared to a placebo.⁸ The use of SSRIs was also linked to suicides in adults;⁹ however, studies have demonstrated that the link between SSRIs and increased suicidality in adults is small or non-significant.¹⁰ There were also reports that some drug manufacturers had misled the public and health regulatory agencies about the safety of these drugs in children and adolescents. In one instance, a leaked internal document from management at GlaxoSmithKline, the manufacturers of Paxil, “advised staff to withhold clinical trial findings in 1998 that indicated the antidepressant paroxetine (Paxil) had no beneficial effect in treating adolescents.”¹¹

In the USA, then attorney general of New York, Eliot Spitzer, launched a lawsuit against GlaxoSmithKline stating the company “committed fraud by withholding negative information and misrepresenting data on prescribing its antidepressant Paxil to children.”¹² Not only was it alleged that GlaxoSmithKline hid clinical trials but also that the company used “a highly selective set of data to promote off-label prescription of the drug to treat children and adolescents.”¹³ This lawsuit illustrated the striking lack of regulation surrounding SSRI use in children and adolescents and “raised troubling

⁷ Benedict W. Wheeler et al, “International impacts of regulatory action to limit antidepressant prescribing on rates of suicide in young people” (2009) 18:7 *Pharmacoepidemiology and Drug Safety* 579 at 579.

⁸ Interview of Dr. Aidan Stokes, Deputy Head of the Dalhousie Department of Psychiatry (12 November 2010) Halifax, Nova Scotia.

⁹ Anonymous, *The Lancet* (14 June 2005) online: *The Lancet* <<http://thelancet.com>>.

¹⁰ Peter Roy-Byrne, “SSRIs and Suicide Risk: A Concern for Adults, Too?” *Journal Watch Psychiatry* (9 March 2005) online: *Journal Watch* <<http://www.jwatch.org>>; Amy Cheung, “Review: SSRIs are associated with increased risk for attempted or completed suicide in adolescents but not in adults or the elderly,” (2009) 150:2 *Annals of Internal Medicine* JC6-13; Carrado Barbui, Eleonora Esposito and Andrea Cipriani, “Selective Serotonin Reuptake inhibitors and risk of suicide: a systematic review of observational studies” (2009) 180:3 *Canadian Medical Association Journal*. Robert Gibbons and J John Mann, “Proper studies of selective serotonin reuptake inhibitors are needed for youth with depression, (2009) 180:3 *Canadian Medical Association Journal*. According to Gibbons and Mann: the FDA extended “the “black box” warning for use of antidepressants” for ages 18-25. The June 2004 Health Canada Warning against SSRI use was directed to patients of all ages, not just patients under the age of 18.

¹¹ Wayne Kondro, “Drug company experts advised staff to withhold data about SSRI use in children” (2004) 170:5 *Canadian Medical Association Journal*.

¹² “Spitzer sues GlaxoSmithKline over Paxil,” *Associated Press* (2 June 2004) online: MSNBC <<http://www.msnbc.msn.com>>; *AG New York v GlaxoSmithKline*, this case was eventually settled out of court; Trudo Lemmens, “Leopards in the Temple: Restoring Scientific Integrity to the Commercialized Research Scene” (2004) 32 *L Med Ethics* 641.

¹³ Lemmens & Bouchard, *supra* note 2 at 335.

questions about the ability of pharmaceutical companies to control and manipulate medical research.”¹⁴ Academic journals such as *The British Medical Journal* (BMJ), conducted reviews of clinical trials of SSRI use in children and adolescents and concluded these trials “had exaggerated the benefits and downplayed the risks.”¹⁵ A review published in *The Lancet* demonstrated that when SSRIs are used in children and adolescents, “the benefits do not outweigh the risks” and that there seemed “to be a systematic bias toward downplaying the suicide issue.”¹⁶ Further studies revealed that not only did SSRI use in children and adolescents result in an increased risk of suicidality, but also that the benefits of SSRIs were very small when compared to a placebo.¹⁷

These reports received a lot of media attention and led to regulatory warnings in many countries. In the USA, consumers launched multiple lawsuits against drug manufacturers, and the Food and Drug Administration (FDA) issued a “black box” warning on SSRI use for children and adolescents—meaning a warning that “appears on a prescription drug’s label and is designed to call attention to serious or life-threatening risks.”¹⁸ This warning cautioned physicians and patients that “antidepressants increase the risk of suicidal thinking and behavior (suicidality) in children and adolescents with major depressive disorder and other psychiatric disorders.”¹⁹ In the UK, the Committee on the Safety of Medicine also released a warning against the use of Paxil in children and adolescents. However, shortly afterwards, the UK Medicine and Healthcare Products Regulatory Agency surmised that all SSRIs, with the exception of fluoxetine (Prozac), should not be used in children and adolescents.²⁰

In Canada, Health Canada issued a warning on February 3, 2004 against the use of SSRIs in children and adolescents. This warning stated that people under the age of 18 “should consult their treating physician to confirm that the benefits of the drug still outweigh its potential risks in light of recent safety concerns.”²¹ These “safety concerns” arose from reports that “some of these drugs may be associated with an increased risk of suicide-related events in patients under 18 years of age.”²² Health Canada released a

¹⁴ *Ibid* at 336.

¹⁵ Leo, *supra* note 5 at 36.

¹⁶ *Ibid* at 37.

¹⁷ *Ibid*.

¹⁸ FDA, Fact Sheet, “A Guide to Drug Safety Terms” online: US Food and Drug Administration <<http://www.fda.gov>>; Jonathan Mahler, “The Anti-Depressant Dilemma” *The New York Times Magazine* (21 November 2004), online: The New York Times <<http://www.nytimes.com>>; Dickman, Hagar. “In the courts: pharma-immunity from paxil-related adolescent suicide suits” (2008) 28:2 Child Legal Rts J 57.

¹⁹ Elizabeth Weller, Sheridan Tucker & Ronald Weller “The Selective Serotonin Reuptake Inhibitors and the Treatment of Depression in children” (2005) 7:2 Current Psychiatry Reports 2005 87 at 88.

²⁰ Stan Kutcher & David M Gardner, “Use of selective serotonin reuptake inhibitors and youth suicide: making sense from a confusing story” (2008) 21 Current Opinion in Psychiatry 65 at 66.

²¹ Health Canada, Advisory, “Health Canada Advises Canadians Under the Age of 18 to Consult Physicians if they are Being Treated with Newer Anti-Depressants”, (Ottawa: Health Canada, 3 February 2004) online: Health Canada <<http://www.hc-sc.gc.ca>>.

²² *Ibid*.

second warning in June 2004:

advising Canadians that SSRIs and other newer anti-depressants now carry stronger warnings. These warnings indicate that patients of all ages taking these drugs may experience behavior and/or emotional changes that may put them at increased risk of self-harm or harm to others.²³

II. THE CURRENT SYSTEM

Off-Label Prescriptions

Currently, Health Canada does not approve the use of SSRIs for children and adolescents; therefore, any SSRI prescribed to children in Canada is prescribed off-label. Physicians very often prescribe off-label drugs for children and adolescents. Since most medicines have only been approved for use in adults, a child suffering from the same condition will often be prescribed the same medication. It has been recognized that "off-label use may represent the only, or best, treatment available for a specific illness in a child."²⁴ Some argue that the term "off-label" would be more accurately described as "silent label" since "the term denotes nothing about health risks or benefits."²⁵

While there are not any SSRIs approved for use in children in Canada, the same is not true in the USA. Shortly after issuing the "black box" warnings on SSRIs for use in children, the Food and Drug Administration approved the use of fluoxetine for the treatment of depression for children between the ages of 12 and 17.²⁶ More recently, the FDA has approved escitalopram for the treatment of depression in adolescents between twelve and seventeen years of age.²⁷ Indeed, subsequent studies showed that while "the therapeutic effect of SSRI treatment in young people below puberty may be insignificant," there is "reasonable evidence to support use of SSRIs as a treatment for adolescent depression and other disorders."²⁸

When prescribing off-label, doctors take into account factors like their own experience, the experiences of their colleagues, and academic literature.²⁹ If a drug is being used for a condition in adults, then doctors tend to use that drug for children and adolescents with the same condition. There are disorders, such as Obsessive Compulsive Disorder, that present the same way in both children and adults, but some disorders manifest differently in children and adults; therefore, one cannot extrapolate the use of the same drug used in

²³ Health Canada, Advisory, "Health Canada Advises Canadians of Stronger Warnings for SSRIs and other Newer Anti-Depressants", (Ottawa: Health Canada, 3 June 2004) online: Health Canada <<http://www.hc-sc.gc.ca>>.

²⁴ Natalie de Paulsen, "The Regulatory Gap: Off-Label Drug Use in Canada" (2005) 63 UT Fac L Rev 183 at para 4.

²⁵ WA Meadows & BD Hollowell, "'Off-label' drug use: an FDA regulatory term, not a negative implication of its medical use" (2008) 20 International Journal of Impotence Research 135 at 140.

²⁶ Ronsley, *supra* note 1 at 219.

²⁷ *Ibid.*

²⁸ Kutcher & Gardner, *supra* note 20 at 68.

²⁹ Stokes, *supra* note 8.

adults for use in children without taking these factors into account.³⁰

Another factor that can influence Canadian doctors when prescribing off-label is the USA's Food and Drug Administration approval or other international regulatory approval. While the FDA does not influence Health Canada, FDA approval of a drug can and does influence individual doctors when prescribing medications.³¹

Finally, the existence of professionally recognized prescribing guidelines also influences the prescribing of medications for off-label uses. For example, the Canadian Psychiatric Association (CPA) (the national professional organization of psychiatrists in Canada) published guidelines in the wake of the 2004 Health Canada warnings. These guidelines describe when and how SSRIs should be prescribed to treat depression and anxiety in children and adolescents. According to these guidelines, "only fluoxetine is considered a first line treatment for depression in children and adolescents"; any other SSRIs:

can be considered as second-line treatments, especially when the depression is severe, chronic, associated with comorbid conditions, and/or when psychosocial treatments such as CBT [Cognitive Behaviour Therapy] have not worked.³²

Further, the CPA guidelines state that the appropriate standard of care in prescribing SSRIs to children involves weekly appointments or telephone contacts for the first month to monitor for adverse effects including suicidality.

The Canadian Academy of Child and Adolescent Psychiatry (CACAP) is the national organization of child and adolescent psychiatrists. It has also published guidelines for the use of SSRIs in children and adolescents. The CACAP "strongly suggest that medication should not be prescribed outside of a comprehensive treatment approach that includes" psychotherapy and psycho-education. However, CACAP acknowledges that "fluoxetine may be the medication of choice for use in both MDD [Major Depressive Disorder] and anxiety disorders."³³ Further, the CACAP cautions that "such as venlafaxine and paroxetine would rarely be recommended and would not be used as first line treatments."³⁴

³⁰ *Ibid.*

³¹ Interview of Dr. David Gardner, Professor with the Dalhousie Department of Psychiatry and College of Pharmacy (12 November 2010) Halifax, Nova Scotia.

³² Raymond W Lam & Sidney H Kennedy, "Prescribing Antidepressants for Depressed in 2005: Recent Concerns and Recommendations" *The Canadian Psychiatric Association* (8 October 2004) online: The Canadian Psychiatric Association <<http://www.cpa-apc.org>>.

³³ E. Jane Garland, Stan Kutcher & Adil Virani, "2008 Position Paper on Using SSRIs in Children and Adolescents" (2009) 18:2 *Journal of the Canadian Academy of Child and Adolescent Psychiatry* 160 at 164.

³⁴ *Ibid.*

III. HOW THE CURRENT SYSTEM FAILS CHILDREN AND ADOLESCENTS

Drug Manufacturers

i) Clinical Testing and Drug Approval

Once a drug is approved by Health Canada for adult use, drug manufacturers have to apply to have the same drug approved for use in a new population or for a new condition. Thus, as SSRIs are approved for use in adults, manufacturers of SSRIs would have to reapply to Health Canada to get the same medications approved for use in children and adolescents. Drug companies are risk adverse and applying to have a drug approved for another population is an additional expense for them.³⁵ Conducting drug trials with children and adolescents is more complex and complicated than drug trials with adults. Since diseases such as depression and anxiety do not start at age eighteen, it is easy for drug companies to assume that their drugs will be used for the same condition in children as in adults even without regulatory approval.³⁶ Indeed, there is a general reluctance on the part of drug companies to conduct clinical drug testing in children.³⁷ In contrast to clinical trials with adults, factors such as parental consent play an important role in clinical trials with children and adolescents. Moreover, “it is difficult to recruit children for clinical trials.”³⁸ This helps explain why before “1997, no published reports demonstrating superior efficacy of SSRIs over placebo in children and adolescents existed.”³⁹

When a drug is prescribed off-label, it means it has not been subjected to the same rigorous standard of testing and review as approved drugs. For a new drug to be approved by Health Canada, it must go through four stages: “Preclinical Studies, Clinical Trials, New Drug Submission and Marketing.”⁴⁰ All these stages must be based on Canadian studies and supportive evidence has to come from Canadian experiences. The *Food and Drugs Regulations* (FDR) divide clinical trials into four different categories, which vary in “size and purpose.”⁴¹ Phases I-III are the clinical trials which determine whether a drug is approved or not, while Phase IV trials occur after a drug has been approved.⁴² It is during Phase IV trials that the “long-term efficacy and safety of the drug” are assessed.⁴³ However, since SSRIs have not been approved for use in children, these medications have not been subjected to Phase IV trials with children and adolescents, and the long-term efficacy of these medications remains unknown. This is particularly troubling since the long-term effects of SSRIs on a child’s emotional,

³⁵ Gardner, *supra* note 31.

³⁶ *Ibid.*

³⁷ *Ibid.*

³⁸ de Paulsen, *supra* note 24 at para 4.

³⁹ Ronsley, *supra* note 1 at 218.

⁴⁰ Lemmens & Bouchard, *supra* note 2 at 321.

⁴¹ *Ibid* at 322.

⁴² *Ibid* at 323 & 322.

⁴³ *Ibid* at 322.

physical and “sexual development” remains unknown.⁴⁴ It is not just the lack of long-term effects of these medications that remain unknown, but many short-term effects as well.

Under the FDR, all clinical trials must follow strict guidelines. For one, clinical trials must be approved by a research ethics board (meaning “a body that is not affiliated with the sponsor”⁴⁵) before a clinical trial begins.⁴⁶ Further, all clinical trials must follow good clinical practices as set down in section C.05.010 of the FDR. A drug manufacturer is required to keep “complete and accurate records” of a clinical trial, including:

records respecting all adverse events in respect of the drug that have occurred inside or outside Canada, including information that specifies the indication for use and the dosage form of the drug at the time of the adverse event.⁴⁷

Research ethics in Canada are also informed by the *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans* (TCPS) of The Interagency Advisory Panel on Research Ethics (PRE).⁴⁸ The TCPS conveys the PRE’s “continuing commitment to the people of Canada to promote the ethical conduct of research involving humans,”⁴⁹ and sets duties upon researchers attempting to conduct research on humans. Article 1.1 states the guiding principles of the TCPS: “respect for persons, concern for welfare and justice.”⁵⁰ The TCPS places a duty on researchers of clinical trials to ensure:

(a) foreseeable risks to participants are minimized, and appropriately evaluated alongside potential benefits, (b) participants are clearly informed as to the nature of these foreseeable risks and potential benefits, (c) participant safety is monitored and accurately reported, and (d) any new information that may impact on the welfare of participants, or their decision to remain involved in a trial, be shared appropriately.⁵¹

The TCPS places similar duties on researchers with regards to consent. According to the

⁴⁴ Nicola Glover-Thomas, “Off-Label Paediatric Drug Use for Juvenile Depression and the Clinical Drug Regulations 2004: The Impact of Available Protective Mechanism” (2008) 29 *Liverpool Law Review* 205 at 207.

⁴⁵ *Food and Drugs Regulations*, CRC c 870 C. 05.001 [FDR].

⁴⁶ *Ibid.*, C.05.010(d).

⁴⁷ *Ibid.*, C.05.012(3)(c).

⁴⁸ Panel on Research Ethics, Fact Sheet, “About us” online: Panel on Research Ethics <<http://www.pre.ethics.gc.ca>>.

⁴⁹ Panel on Research Ethics, *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans*, “Introduction,” online: Panel on Research Ethics <<http://www.pre.ethics.gc.ca>>.

⁵⁰ Panel on Research Ethics, *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans*, “Chapter 1,” online: Panel on Research Ethics <<http://www.pre.ethics.gc.ca>>.

⁵¹ *Ibid.*, Chapter 11.

TCPS, for children to participate in clinical trials, researchers must obtain consent from “authorized third parties in accordance with the best interests of the persons concerned.”⁵²

Currently, most of the clinical trials of SSRI use in children and adolescents are smaller trials sponsored by drug manufacturers.⁵³ Although some of these trials may provide as rigorous and thorough of an assessment as ones conducted under the FDR requirements, there is great potential for the results of these trials to be biased or skewed when compared to those conducted for Health Canada approval. This is very troubling since, as demonstrated in Part II of this paper, manufacturers of SSRIs have in the past misled the public and regulators about data from their clinical trials.

ii) **Manufacturer Liability and the Learned Intermediary**

In the USA, most of the lawsuits involving manufacturers of SSRIs and children concern severe side effects that arose from off-label use. Cases such as, *Miller v Pfizer*, are multifold in the USA. In *Miller*, the parents of a thirteen-year-old boy who killed himself while taking Prozac unsuccessfully sued the manufacturers of Prozac, Pfizer, alleging that Prozac made their son suicidal.⁵⁴ In *O’Neal v SmithKline Beechman Corporation*, the plaintiff sued the makers of Paxil alleging the company should have warned the public about increased risks of suicidality in children and adolescents when taking Paxil. The plaintiff’s son was prescribed Paxil and attempted suicide, later dying from his injuries. The case was dismissed because the plaintiff’s son had died seven years before the Food and Drug Administration issued its black box warning and required manufacturers to include information about increases in suicidality on their packaging.⁵⁵ In *Hoorman v SmithKline*, the plaintiffs launched a class action suit against the makers of Paxil, alleging the company “used its marketing and sales force to encourage doctors to prescribe Paxil off-label to pediatric patients.” *Hoorman* settled outside of court with the plaintiff’s “out-of-pocket expenses related to their Paxil purchase” refunded and without the company admitting any wrongdoing. After the settlement, the defendants continued to maintain: “Paxil was prescribed off-label based solely on the discretion of doctors.”⁵⁶

By contrast, Canadian case law is sparse in this area and there have been no Canadian lawsuits involving patients or their parents suing manufacturers of SSRIs for adverse side effects they experienced. The leading Canadian case on the liability of manufacturers of medical products is *Hollis v Dow Corning*. In *Hollis*, the Supreme Court of Canada noted that there is often a power imbalance between patients and

⁵² *Ibid*, Chapter 3, article 3.9.

⁵³ Gardner, *supra* note 31.

⁵⁴ *Miller v Pfizer, Inc*, 356 F (3d) 1326 (10th Cir 2004); Jonathan Mahler, “The Anti-Depressant Dilemma” *The New York Times Magazine* (21 November 2004), online: The New York Times <<http://www.nytimes.com>>.

⁵⁵ *O’Neal v SmithKline Beechman Corporation*, 551 F Supp (2d) 993 (2008); Dickman, Hagar. “In the courts: pharma-immunity from paxil-related adolescent suicide suits” (2008) 28:2 Child Legal Rts J 57 at 58.

⁵⁶ *Ibid. Hoorman, et al v GlaxoSmithKline Beecham Corp.*, 04-L-715 (Ill Cir Cr 2006).

manufacturers, or patients and physicians; therefore manufacturers have a duty to warn consumers of any dangers associated with their product.⁵⁷ This duty creates “a heavy onus on manufacturers of medical products” due to the “intimate relationship between medical products and the consumer’s body.”⁵⁸ Further, this duty:

serves to correct the knowledge imbalance between manufacturers and consumers by alerting consumers to any dangers and allowing them to make informed decisions concerning the safe use of the product.⁵⁹

Although *Hollis* involved the manufacturer of breast implants, and not off-label uses of medication, it still provides a framework upon which future claims of liability against drug manufacturers for the experience of severe side-effects from the off-label use of their product may be based.

A recent case decided by the Ontario Supreme Court, *Goodridge v Pfizer Canada Inc.*,⁶⁰ may perhaps provide the most illustrative example as to how Canadian courts might approach the issue of manufacturer liability for severe side effects caused by off-label drug prescriptions. In *Goodridge*, a group of plaintiffs attempted to launch a class action lawsuit against Pfizer, the maker of the drug Neurontin, as well as the manufacturers of the generic version of the drug. Neurontin is approved by Health Canada for the treatment of epilepsy. The plaintiffs were prescribed Neurontin off-label for treatment of pain and alleged they experienced suicidal behavior while taking the drug. The plaintiffs alleged Pfizer was negligent “to Neurontin consumers by falsely and wrongfully promoting Neurontin for ‘off-label’ uses” and by “designing and distributing a drug that was useless for its off-label uses.”⁶¹ The court noted the standard set down in *Hollis* is useful for assessing negligence by drug manufacturers concerning the duty to warn consumers of dangers associated with their product.

In *Goodridge* and *Hollis*, the courts noted a manufacturer’s duty to warn consumers can be dismissed if the manufacturer gives “an adequate warning to a ‘learned intermediary,’” such as a physician.⁶² When dealing with prescription drugs:

the duty of manufacturers to warn consumers is discharged if the manufacturer provides prescribing physicians, rather than the consumers, with an adequate warning of the potential dangers associated with the use of the drug.⁶³

⁵⁷ *Hollis v Dow Corning Corp.*, [1995] 4 SCR 634 at para 21, 129 DLR (4th) 609 [*Hollis*].

⁵⁸ *Ibid* at para 23.

⁵⁹ *Ibid* at para 21.

⁶⁰ *Goodridge v Pfizer Canada Inc.*, 2010 ONSC 1095, [2010] OJ No 655 [*Goodridge*]. In *Goodridge*, the plaintiffs made a motion seeking a certificate of class action against the Defendants, and the Defendants made a motion to strike out part of the Plaintiff’s statement of claim. The Plaintiffs were granted their certificate and the Defendants were successful in striking out portions of the Plaintiff’s statement of claim.

⁶¹ *Ibid* at para. 5.

⁶² *Hollis*, *supra* note 57 at para 85.

⁶³ *Ibid*.

Underlying this rule, is that if a patient is primarily reliant on:

the judgment of a learned intermediary and not the manufacturer of the product, then the manufacturer will satisfy its duty to warn the consumer by adequately warning the learned intermediary of the risks inherent in the use of the product.⁶⁴

Thus, in a lawsuit, the manufacturers of SSRIs could argue they discharged their duty to the patient by providing sufficient warnings about increases in suicidality or other severe side effects to the patient's physician, thereby avoiding liability.

Health Canada

i) Post-Approval Marketing and Off-Label Drugs

Health Canada is the regulatory body responsible for food and drug products in Canada. The Therapeutic Products Directorate (TPD), through the *Food and Drugs Act* (FDA) and the FDR, assesses the safety and effectiveness of medications.⁶⁵ Health Canada only regulates on-label drugs, i.e. drugs that they have approved for use. Thus, the use of SSRIs in children and adolescents is not specifically monitored by Health Canada since these drugs are prescribed off-label. However, Health Canada does in a sense monitor off-label uses of a drug through post-approval monitoring to make sure drug companies comply with the FDA and the FDR.⁶⁶

One of the ways in which Health Canada monitors drugs after approval is through "post-market surveillance,"⁶⁷ which involves gathering "reported adverse reactions that occur after drug use."⁶⁸ The FDR defines adverse reactions as: "a noxious and unintended response to a drug, which occurs at doses normally used or tested for the diagnosis, treatment or prevention of a disease or the modification of an organic function."⁶⁹

These adverse reactions are not confined to reactions arising from on-label uses, but also include adverse reactions from off-label uses as well. Section C.01.016 of the FDR stipulates that if during any clinical trials a drug manufacturer becomes aware of any drug reaction or any adverse drug reaction, the manufacturer must:

(a) a report of all information in respect of any serious adverse drug reaction that has occurred in Canada with respect to the drug, within 15 days after receiving the information; and (b) a report of all information

⁶⁴ *Ibid.*

⁶⁵ Lemmens & Bouchard, *supra* note 2 at 319.

⁶⁶ Paulsen, *supra* note 24 at para 17.

⁶⁷ *Ibid* at para 18.

⁶⁸ *Ibid* at para 21.

⁶⁹ *FDR*, *supra* note 45 C 01.001.

in respect of any serious unexpected adverse drug reaction that has occurred outside Canada with respect to the drug, within 15 days after receiving the information.

Section C.01.017 of the FDR makes drug manufacturers legally required to “maintain records of the reports and case reports” of adverse reactions. Patients and healthcare professionals can also report adverse reactions, however, this is done on a voluntary basis. Patients can fill out the “Consumer Side Effect Reporting Form” describing their adverse reactions and physicians can fill out the “Canada Vigilance Adverse Reaction Reporting Form.”⁷⁰ Given that physicians only report adverse effects on a voluntary basis, potentially, adverse effects not reported by drug manufacturers could remain undetected and comprise public safety.

The Canadian Adverse Reaction Information System (CADRIS) collects this data and analyzes it to “discover potential health product safety signals.”⁷¹ The discovery of a signal is “considered to be the preliminary indication of a product-related issue.”⁷² Before any regulatory action is taken against a drug, adverse reactions need to undergo a “preliminary evaluation” which considers:

the frequency, severity, plausibility, quality of the information contained in the reports, amount of product used, time needed for appearance of the reaction, underlying diseases, simultaneous use of other medications, and evidence of disappearance or reappearance of the reaction once the product was discontinued or reintroduced.⁷³

Thus, a reaction that is considered to be very “severe” might not be subject to regulatory action if this reaction has occurred in only a small number of patients. Placing emphasis on the “severity” of a reaction can have serious consequences for children and adolescents, since less severe reactions could have potential long-term consequences on their development. If a strong “signal” is identified, Health Canada has a variety of regulatory responses available to it, such as: post-marketing studies; “dissemination of information to healthcare professionals and consumers (e.g. letters, advisories, publications, specialized internet sites); “product labeling changes (including addition of contraindications, warnings, precautions or supplementary AR information on the product information or Product Monograph); “issuing of public alerts”; and “conducting market withdrawals.”⁷⁴ Further, a medication’s monograph must include “any potential side effects.”⁷⁵ One could argue that the 2004 Health Canada warnings against the use of SSRIs in children demonstrate that the current regulatory system

⁷⁰ Health Canada, Fact Sheet, “Adverse Reaction Reporting” online: Health Canada <<http://www.hc-gc.ca>>.

⁷¹ Health Canada, Fact Sheet, “Adverse Reaction Information” online: Health Canada <<http://www.hc-gc.ca>>.

⁷² *Ibid.*

⁷³ *Ibid.*

⁷⁴ Health Canada, *supra* note 71.

⁷⁵ Lemmens & Bouchard, *supra* note 2 at 330; Canada, Health Products and Food Branch, Report, “Blueprint for Renewal: Transforming Canada’s Approach to Regulating Health Products and Food,” (October 2006) online: Health Canada <<http://www.hc-sc.gc.ca>>.

works efficiently and protects the public. Once the adverse reactions of increased suicidality were identified, Health Canada responded by issuing a public warning concerning the existence of these symptoms.

ii) Health Canada Proposals for Reform

The weaknesses in the current regulatory system regarding off-label uses of medication have not gone unnoticed by Health Canada. *Blueprint for Renewal: Transforming Canada's Approach to Regulating Health Products and Food* was released by Health Canada in 2006 as a proposal on how to change the current regulatory system.⁷⁶ The *Blueprint* proposes “placing a risk-benefit framework at the forefront of the regulatory approval process, replacing the current FDA and regulations with new legislation.”⁷⁷ Notably, the proposal “expresses a clear concern for patient safety” and attempts to address the inadequacy of the current regulatory system regarding post-approval monitoring of drugs.⁷⁸ Proposed improvements include: “‘probationary’ regulatory approval contingent on post-marketing surveillance of adverse effects,” “jurisdiction to require sponsors to conduct post-market studies” and “initiatives to address under reporting of post-marketing adverse effects.”⁷⁹

In 2008, many of the proposals of the *Blueprint for Renewal* were incorporated into *Bill C-51- An Act to amend the Food and Drugs Act*. The bill, however, has not yet been passed by parliament.⁸⁰ Thus, the proposed changes to the regulatory process have not been adopted. If adopted, they would make welcome changes to the post-approval regulation of drugs and place more responsibility on drug manufacturers to continuously monitor their product to ensure that their drugs are safe for patients. Nevertheless, even if the *Blueprint for Renewal* were adopted in full, there would still be problems with off-label drug use. The proposed changes appear to be directed at on-label uses, thus still leaving the issues of off-label prescribing unchanged and mainly unregulated.

iii) Health Canada Does Not Regulate The “Practice of Medicine”

One of the biggest problems with the current regulatory system is that the practices of medicine and pharmacy are the domain of the provinces, territories and the provincial Colleges of Physicians and Registrars of Pharmacy.⁸¹ Health Canada “has no jurisdiction over how health care professionals prescribe drugs once they are approved.”⁸² Even the local regulatory bodies leave doctors with a great deal of discretion when prescribing medication. According to Health Canada: “a physician's

⁷⁶ *Ibid* at 361.

⁷⁷ *Ibid*.

⁷⁸ *Ibid*.

⁷⁹ *Ibid* at 362.

⁸⁰ Canada, Bill C-51, *An Act to amend the Food and Drugs Act and to make consequential amendments to other Acts*, 2nd Sess, 39th Parl, 2008 (debates at second reading 10 June 2008).

⁸¹ Canada, Health Products and Food Branch, Report, “Response to Recommendations to Health Canada of the Coroner’s Jury into the Death of Ashley Marie Atkinson” (29 July 2003), online: Health Canada <<http://www.hc-sc.gc.ca>>.

⁸² *Ibid*.

decision to prescribe particular medication for an individual patient be it for an indication listed on an approved drug's labeling or otherwise, is part of the 'practice of medicine.'"⁸³ Thus, Health Canada has no regulatory authority over the ability of physicians to prescribe medications off-label. This is especially troubling for medications that Health Canada has issued a warning against. Although Health Canada has issued warnings about the use of SSRIs in children, these medications are still widely prescribed in children. Essentially, due to the great deal of discretion physicians possess to prescribe medications, Health Canada warnings lack strength and are rendered almost meaningless.

Physicians

i) The Standard of Care

Whether or not physicians should be held liable for prescribing SSRIs to children and adolescents should be assessed through medical negligence. For a negligence claim to succeed, a plaintiff has to show:

- (a) the defendant owed the plaintiff a legal duty of care;
- (b) the defendant breached that duty of care;
- (c) the plaintiff suffered legally recognized damage;
- and (d) the damage was caused by the defendant's breach of the duty of care.⁸⁴

In medical negligence claims, the standard of care doctors owe their patients is usually assessed with regards to the standards practiced by the majority in the profession. The leading Canadian case regarding the standard of care doctors owe to their patients is *Ter Neuzen v Korn*. Here the Supreme Court concluded:

It is well settled that physicians have a duty to conduct their practice in accordance with the conduct of a prudent and diligent doctor in the same circumstances. In the case of a specialist, such as a gynecologist and obstetrician, the doctor's behaviour must be assessed in light of the conduct of other ordinary specialists, who possess a reasonable level of knowledge, competence and skill expected of professionals in Canada, in that field.⁸⁵

Thus, a specialist like a psychiatrist, "who holds himself out as possessing a special degree of skill and knowledge, must exercise the degree of skill of an average specialist in his field."⁸⁶ To assess whether a psychiatrist breached the standard of care to a child or adolescent patient by prescribing SSRIs, one needs to assess the average practice of psychiatrists in similar circumstances. Psychiatrists, particularly child psychiatrists, will

⁸³ *Ibid.*

⁸⁴ Bernard Dickens, "Medical Negligence" in Jocelyn Downie, Timothy Caulfield & Colleen M Flood eds, *Canadian Health Law and Policy* (Markham: LexisNexis, 2007) 102 at 103.

⁸⁵ *ter Neuzen v Korn*, [1995] 3 SCR 674 at para 33, 127 DLR (4th) 577.

⁸⁶ *Ibid.*

presumably be held to a higher standard than family physicians because they possess “a special degree of skill and knowledge” regarding mental health problems and disorders in children and adolescents, as well as psychopharmacology use in these populations. Family physicians will not be presumed to have similar knowledge since they do not receive the same advanced training in the area, as do psychiatrists.

One way to assess whether a physician is complying with the standard of care is to determine if they are following guidelines set by professional organizations such as the CPA and the CACAP.⁸⁷ If a physician does not follow such guidelines, they are “vulnerable to liability for negligence.”⁸⁸ The guidelines from CPA and CACAP concerning prescribing SSRIs to children appear to be closely followed at least by psychiatrists. In accordance with these guidelines, the first and most widely prescribed SSRI in children and adolescents is Prozac. One study found that the “SSRI usage by psychiatrists in the inpatient setting more closely reflects” professionally recognized guidelines, “than does usage in the outpatient setting.”⁸⁹ However, the guidelines from the CPA and the CACAP both deal with medications that have not been approved for use in children by the country’s chief medical regulatory body, Health Canada. Surprisingly, it appears that guidelines from professional associations carry more weight when assessing the standard of care than do warnings issued by Health Canada.

ii) Family Physicians

The guidelines from the CPA and CACAP are of limited use since these guidelines are really only binding on the members of those bodies. However, most prescribers of SSRIs are family doctors and not members of those bodies.⁹⁰ Consequently, many family physicians do not follow these guidelines and are thus acting in a potentially negligent manner when prescribing SSRIs to children and adolescents. This is particularly troubling because the guidelines advise physicians not to prescribe certain SSRIs, most notably Paxil, due to the increased risk of suicidality in children and adolescents. Nonetheless, many family physicians do follow the professionally approved standard of care in providing weekly follow-ups and very slow increases in doses.⁹¹ Many family doctors simply do not know about these guidelines, thus there is a need for these doctors to be more aware of these guidelines.⁹²

Although many family physicians are unaware of the CPA and the CACAP guidelines concerning prescribing SSRIs to children, most are aware of the 2004 Health Canada warnings. One of the consequences of the warnings has been that many family doctors simply refuse to prescribe these medications to children.⁹³ This concern was discussed much earlier in Health Canada’s “Scientific Advisory Panel on Selective Serotonin

⁸⁷ Dickens, *supra* note 84 at 111.

⁸⁸ *Ibid.*

⁸⁹ Ronsley, *supra* note 1 at 224.

⁹⁰ Stokes, *supra* note 8.

⁹¹ *Ibid.*, Dr. Stokes found that most family physicians practicing in rural Nova Scotia practiced the same standard of care as doctors in Halifax.

⁹² Gardner, *supra* note 31.

⁹³ Stokes, *supra* note 8.

Reuptake Inhibitors and Serotonin/Norepinephrine Reuptake Inhibitors” in 2004. In this panel, there were concerns that “some non-specialist physicians who see the warning are over sensitive and may not prescribe, or conversely they may ignore the warnings.”⁹⁴ However, it remains to be seen whether a family physician who does not follow professional guidelines but follows the Health Canada warnings and does not prescribe SSRIs to children would be liable for negligence.

The duty of care of family physicians, when confronted with depressed or anxious children patients, may involve a duty to refer them to a psychiatrist or another physician who has more training in this area. Dickens has shown that physicians “may have a duty of care not to treat their patients, but promptly to refer them to colleagues whose skills are more suited to the patients’ needs.”⁹⁵ Since psychiatrists have more advanced knowledge than family physicians on how to treat depression and anxiety, they are better equipped to deal with children and adolescent patients suffering from these ailments. The failure of a family physician or other non-specialist physician to refer a child to a more suitable specialist can be considered a breach in the standard of care. Consequently, this would be seen as negligent since “physicians are expected to be aware of the limits of their own skills, and to recognize the general limits of the facilities in which they practice, although not necessarily on a case-by-case basis.”⁹⁶ Yet, family physicians remain the top prescribers of SSRIs to children, which suggests they are treating the children themselves instead of referring them to see a psychiatrist.

iii) The Locality Rule

However, psychiatrists or physicians with in-depth knowledge of childhood mental disorders are often not available in the location in which a patient resides. Even if a patient resides in an area with psychiatrists, there may not be psychiatrists who specialize in child psychiatry and the patient may have to wait months to get an appointment. While the first line of treatment in children is cognitive-behaviour therapy, most physicians who prescribe SSRIs for children are family practitioners who lack the resources to provide this therapy.⁹⁷ In the past, a physician’s standard of care was measured against “like practitioners in the area.”⁹⁸ This was known as the “locality rule.” However, this rule has largely fallen out of favour. One of the problems of the locality rule was addressed in *Sunnucks v Tobique Valley Hospital*, where the court noted “The danger is that the rural-urban distinction might create a double standard based on geography allowing inferior health care to be considered adequate in some areas.”⁹⁹

Due to the fact that Canadian Medicare and the *Canada Health Act* provide for equal access of all Canadians to receive medical care, “it appears inequitable that residents of

⁹⁴ Health Canada, Report, “Scientific Advisory Panel on Selective Serotonin Reuptake Inhibitors and Serotonin/Norepinephrine Reuptake Inhibitors” (20 February 2004), online: Health Canada <<http://www.hc-sc.gc.ca>>.

⁹⁵ Dickens, *supra* note 84 at 104.

⁹⁶ *Ibid* at 110.

⁹⁷ Stokes, *supra* note 8.

⁹⁸ Dickens, *supra* note 84 at 109.

⁹⁹ *Sunnucks v Tobique Valley Hospital*, [1999] NBJ No 344 at 71, 216 NBR (2d) 201.

one locality may have less entitlement to a given standard of care than residents of other localities in the same province.”¹⁰⁰ Thus, the inability for children to receive treatment from a psychiatrist or a psychologist, or to receive similar treatment as to that provided by a psychiatrist, is a breach of the standard of care. Whereas a psychiatrist prescribing SSRIs to children patients will follow the CPA and the CACAP guidelines, a family physician is under no obligation to follow these guidelines when prescribing SSRIs to children and adolescents. This creates an inequality in the treatment provided to children and adolescents, which could have dangerous long-term consequences for the patient. However, it remains to be seen whether a physician would be held liable for not referring a child or adolescent patient to a psychiatrist or psychologist if there is none in their community.

Patients and Their Parents

i) Age of Consent

Another major issue arising from prescribing of SSRIs to children is informed consent. According to Rozovsky:

for consent to be valid, the following criteria must be met:

1. The patient must be legally competent to consent to treatment.
2. The patient must possess the mental capacity to authorize care.
3. The patient must receive a proper disclosure of information from the care-giver.
4. The authorization should be specific to the procedure to be performed.
5. The patient should have an opportunity to ask questions and to receive understandable answers.
6. The authorization obtained should be free of undue influence and coercion.
7. The authorization obtained should be free of misrepresentation of material information.¹⁰¹

One of the requirements for informed consent is that the patient must possess the mental capacity to make a decision about their medical treatment. Consequently, when dealing with patients who are under the age of majority issues of mental capacity arise. While “the law presumes that all patients—including children—are legally competent to give an authorization for treatment,” the age of the child will certainly be a factor in assessing capacity.¹⁰² The age of consent is not considered to be the age of majority.¹⁰³

The legal ability of patients under the age of eighteen to make their own decisions about medical treatments varies from province to province. Many provinces have enacted

¹⁰⁰ Dickens, *supra* note 84 at 109.

¹⁰¹ Lorne Elkin Rozovsky, *The Canadian Law of Consent to Treatment* (Markham: LexisNexis Butterworths, 2003) at 6.

¹⁰² *Ibid* at 7.

¹⁰³ *Ibid*.

legislation that specifies the age of consent while other jurisdictions use the “mature minor” rule.¹⁰⁴ This rule does not rely solely on a child’s age but allows the law to decide if children have the capacity to make treatment decisions such as whether or not to take SSRIs, on a case-by-case basis.¹⁰⁵ The mature minor has been defined as “one with the capacity to understand the nature and consequences of medical treatment. Such a person has the power to consent to medical treatment and parental consent is not necessary.”¹⁰⁶ Factors courts will look at to determine whether a child is a mature minor include: “age, maturity level, nature and extent of the minor’s dependence on parents and the complexity of the treatment.”¹⁰⁷ Arguably, an adolescent will likely be deemed a mature minor when the treatment involves taking SSRIs, since this form of treatment is not as evasive or “complex” as surgery or treatment for cancer. If a child is deemed to be a mature minor, then physicians have the onus “to get to know their patient—just as it does in the adult treatment context.”¹⁰⁸

ii) Lack of Available Information for Patients and Parents

If a child is deemed to be a mature minor and able to make their own decisions concerning whether or not to take SSRIs as a treatment for anxiety or depression, serious challenges still exist. Since SSRIs are a form of psychiatric treatment, a mature minor could face further difficulties as their mental capacity to make treatment decisions while suffering from a mental illness could be challenged. Further, “Youth-centred education and information tools” that support “knowledge sharing, shared decision-making, and facilitation of monitoring” of these types of medicines are largely unavailable. Informing children and adolescents about the risks and benefits of SSRIs is crucial because “the warnings and the media response invoked a fear of diagnosis and treatment among patients.”¹⁰⁹

The need for youth to be well informed about SSRIs is especially necessary since many youth use the Internet to find information about medications. This is problematic because of the

potential lack of youths’ ability to evaluate websites, overwhelming information volume, uncertain credibility, incomplete information, inappropriate literacy levels, and the potential for those with medical conditions to be taken advantage of, is not uncommon with use of the Internet.¹¹⁰

¹⁰⁴ *Ibid* at 8; provinces such as Quebec and New Brunswick have legislation that specifies the age of consent at ages 14 and 16 respectively.

¹⁰⁵ *Ibid*.

¹⁰⁶ *Chmiliar v Chmiliar*, 2001 ABQB 525 at para 44, 295 AR 140.

¹⁰⁷ Rozovsky, *supra* note 101 at 82.

¹⁰⁸ *Ibid* at 8.

¹⁰⁹ Andrea Murphy et al, “Collaborating with Youth to Inform and Develop Tools for Psychotropic Decision Making” (2010) 19:4 *Journal of the Canadian Academy of Child and Adolescent Psychiatry* 256 at 262.

¹¹⁰ *Ibid* at 258.

Without proper informational tools that allow children and adolescents to evaluate the risks and benefits of SSRIs, and that take into account the maturity, literacy, cognitive and intellectual abilities of these age groups, children and adolescents cannot to be said to have enough information to give informed consent.

In the United States, the Food and Drug Administration's website contains "medication guides" which are guides written specifically for the consumer and which detail the proper use of the drug and serious side effects.¹¹¹ The FDA's website also contains a specific section for "antidepressant use in children, adolescents and adults" which highlights that these medications are subject to "black box" warnings due to increased risks of suicidality. It also contains detailed medication guides for most major antidepressant medications.¹¹²

Health Canada's website contains no such detailed guides for patients and their parents. Although Health Canada's website does contain drug information, it is not easily accessible to the public as drugs need to be searched according to their Drug Identification Number or Anatomical Therapeutic Chemical.¹¹³ However, since 2005 Health Canada has operated an online Adverse Reaction Database, allowing health care professionals and patients "easier access to information about adverse drug reactions."¹¹⁴ Nonetheless, there is still a void in easily accessible information about SSRIs written for patients and their parents.

iii) Informed Consent and Off-Label Prescriptions

Issues surrounding informed consent are also raised due to the off-label status of SSRIs for use in children. For a patient or a patient's parent to give informed consent, they must receive a sufficient and adequate amount of information on which to base their decision.¹¹⁵ The issue that arises with SSRI use in children is whether or not a physician should disclose the off-label status of these medications, i.e. that these medications have not been approved for use in children. However, Canadian case law is silent about "what a doctor is required to disclose when prescribing a drug for an off-label use."¹¹⁶ Here again American case law is more developed. In *Klein v Biscup*, the plaintiff sued her physician for failing to tell her that the "devices used for her back surgery were not approved by the FDA."¹¹⁷ The Court of Appeal concluded a physician does not have a duty to inform a patient about the off-label status of a drug or device and that "off-label use of a medical device is not a material risk inherently involved in a proposed therapy which a physician should disclose to a patient prior to the therapy."¹¹⁸ In a similar case,

¹¹¹ Food and Drug Administration, "Medication Guides" online: US Food and Drug Administration <<http://www.fda.gov>>.

¹¹² Food and Drug Administration, Fact Sheet, "Antidepressant Use in Children, Adolescents and Adults," online: US Food and Drug Administration <<http://www.fda.gov>>.

¹¹³ Health Canada, "Drug Product Database," online Health Canada <<http://www.hc-sc.gc.ca>>.

¹¹⁴ Lemmens & Bouchard, *supra* note 2 at 341.

¹¹⁵ Rozovsky, *supra* note 101 at 13.

¹¹⁶ Paulsen, *supra* note 24 at 39.

¹¹⁷ Meadows, *supra* note 25 at 141. *Klein v Biscup*, 109 Ohio App (3d) 855 (1996).

¹¹⁸ *Ibid*.

Southard v Temple University Hospital, the court “held that a physician’s failure to inform a patient of the FDA’s classification of a device was not a failure to obtain a patient’s informed consent.”¹¹⁹

In *Reibl v Hughes*, the Supreme Court of Canada concluded informed consent should be determined by “what the average prudent person, the reasonable person in the patient’s particular position, would agree to or not agree to, if all material and special risks of going ahead with the surgery or foregoing it were made known to him.”¹²⁰ Even “if a certain risk is a mere possibility which ordinarily need not be disclosed, yet if its occurrence carries serious consequences, as for example, paralysis or even death, it should be regarded as a material risk requiring disclosure.”¹²¹

While informed consent does not involve the disclosure of every risk, it does require a physician to disclose the risks that would most likely affect a patient’s decision to undergo that treatment.¹²² In *Ciarlariello v Schacter*, the Supreme Court of Canada concluded the test for informed consent “focuses on what the patient would want to know,” and “the crucial question in determining the issue is whether a reasonable person in the patient’s position would want to know of the risk.”¹²³ A patient and/or their parents would most likely want to know that a drug proposed by their physician has not been approved the country’s drug regulatory body. Knowing the off-label status of a drug, and the reasons why it is not approved, are reasonable requests that would satisfy the *Ciarlariello* test for informed consent.

iv) Alternative Treatment Options

Not only should a patient be informed about the risks and benefits of a particular treatment, but also about the risks and benefits of any alternative treatment options.¹²⁴ An alternative treatment option to SSRI use should be psychotherapy, specifically cognitive-behaviour therapy. Whether an alternative treatment will be considered reasonable depends on “the risk and benefits of the alternative intervention” as well as “the availability of the alternative test or treatment, and what is reasonable given the circumstances of the particular patient.”¹²⁵ Psychotherapy might not be a reasonable alternative to many patients since they might not live in an area where there are psychologists. Even if they do, it could take many months to see a psychologist. If a patient is suicidal or severely depressed, waiting that long for treatment might not be the “best” option. Further, the only available psychologists may be private, an option many patients might not be able to afford. It is unreasonable to expect family doctors to give psychotherapy given their hectic workload. Essentially, “the patient is entitled to know about the alternatives and the risks and advantages of each.”¹²⁶ The patient and/or their

¹¹⁹ *Ibid*; *Southard v Temple University Hospital*, 756 A (2d) 670 (2000).

¹²⁰ *Reibl v Hughes*, [1980] 2 SCR 880 at 899, 114 DLR (3d) 1 [*Reibl*].

¹²¹ *Martin v Inglis*, 2002 SKQB 157 at para 90, [2002] 9 WWR 500.

¹²² Rozovsky, *supra* note 101 at 14.

¹²³ *Ciarlariello v Schacter*, [1993] 2 SCR 119 at 133, 100 DLR (4th) 609.

¹²⁴ Rozovsky, *supra* note 101 at 18.

¹²⁵ *Ibid*.

¹²⁶ *Ibid* at 19.

parents can only make an informed decision after they have received this information. However, this does not appear to be happening in Canada as “concerns about the risk of suicide in youth have led not only to fewer SSRI prescriptions without substitution of alternative medications or psychotherapies.”¹²⁷

IV. PROPOSAL FOR REFORM

Despite the 2004 Health Canada warnings and the surrounding media attention, there is evidently still more work to be done. There is a glaring need for drug manufacturers, regulatory agencies and physicians to be more accountable and transparent. A good starting point for reform would be to hold drug manufacturers strictly liable if they discovered severe adverse reactions and side effects from their medications, either during Health Canada clinical trials or independent clinical trials, and did not report them to Health Canada. Strict liability would serve as a deterrent to drug manufacturers against not reporting these reactions and side effects and would help ensure that patients, parents, physicians and regulatory bodies are aware of any potential dangers associated with the use of a drug.

Secondly, warnings issued by Health Canada should be considered when assessing a physician’s standard of care. Moreover, these warnings should be given more weight when a physician is considering appropriate treatments for a patient and physicians should not be able to simply disregard these warnings. Although there are valid uses for off-label prescribing in adults, extra caution should be exercised for children and adolescent patients. Off-label prescribing of drugs should still be used in children in emergency situations, or where there is no other medical alternative.

However, if Health Canada has issued warnings against the use of a medication or class of medications, such as SSRIs, off-label prescribing of these medications should not occur. Given that there are other forms of treatment, such as cognitive behavioral therapy, that do not carry such inherent risks as SSRIs, the use of an unapproved class of drugs that have been subjected to governmental warnings should not be seen as a “reasonable” form of treatment. Consequently, there needs to be an increased availability of cognitive-behaviour therapy for children and adolescents. Until there are multiple long-term studies, preferably conducted by a neutral party such as Health Canada, and conducted in accordance with the principles of the TCPS, demonstrating that the benefits of SSRIs in children outweigh the risks, SSRIs should simply not be prescribed to children and young adolescents.

Nonetheless, SSRIs could still be prescribed to older adolescents provided they are prescribed prudently and cautiously. SSRIs have different effects on pre-pubescent children in comparison to older adolescents, especially adolescents approaching the age

¹²⁷ Robert Gibbons & J. John Mann, “Proper studies of selective serotonin reuptake inhibitors are needed for youth with depression” *Canadian Medical Association Journal* (3 February 2009), online: Canadian Medical Association <<http://www.cmaj.ca>>.

of majority.¹²⁸ Given the vulnerable nature of this population, physicians should exercise a higher standard of care when prescribing SSRIs to adolescents as opposed to prescribing SSRIs to adults. At minimum, adolescents and their parents need to be better informed. Specifically, patients and their parents need to be made aware of the off-label status of SSRIs and that no SSRIs have been approved by Health Canada for use in people under the age of eighteen. Physicians should also advise patients that many of the long-term risks of SSRIs are unknown and that there have been no Health Canada approved SSRI drug trials. Disclosing the off-label status of SSRIs for use in adolescents should be considered a material risk to a patient. Not disclosing the off-label status of these medications should be seen as a deviation from the standard of care and physicians should be held liable for this nondisclosure.

Further, physicians should be required to notify patients and parents to be extra vigilant in monitoring side effects, most notably for increases in suicidality. Family physicians need to become more aware of prescribing guidelines from national associations such as CPA and the CACAP. These associations should hold continuing education sessions to provide family physicians with opportunities to learn about these guidelines. Provincial Colleges of Physicians and Surgeons could increase the awareness of these guidelines by adopting them themselves, as this would also make these guidelines binding on family physicians. However, despite these recommendations, the question remains whether knowing the off-label status of SSRIs and that many of the risks associated with SSRIs are still unknown enables a patient or their parents to make a true informed consent to treatment.

CONCLUSION

Depression and anxiety are two of the most prevalent disorders in the world. The need for safe and effective medications to combat these disorders is great. Therefore, it is not surprising that the emergence of SSRIs led some to “believe SSRIs have been to depression what antibiotics once were to bacterial infections – ‘miracle drugs.’”¹²⁹ While SSRIs have successfully helped many adults combat depression and anxiety, the same cannot be said about children. For many children and adolescents, the use of SSRIs to treat depression and anxiety has paradoxically led to an increase in suicidality. Yet, surprisingly, almost a decade after the reports and studies showing this increase in suicidality, little has been done and children and adolescents are still widely prescribed these medications.

The continued use of SSRIs in children and adolescents is even more surprising given there are government regulations in multiple countries and continents which warn against the use of SSRIs in children and adolescents. In Canada, SSRIs are still

¹²⁸ Kutcher & Gardner, *supra* note 20 at 68; Ronsley, *supra* note 1; SE Hetrick et al., “Selective Serotonin Reuptake Inhibitors (SSRIs) for depressive disorders in children and adolescents” (2008) 3 Evidence-Based Child Health: A Cochrane Review Journal at 829- 830; CL Donnelly et al, “Sertaline in children and adolescents with major depressive disorder” (2006) 45:10 Journal of the American Academy of Child and Adolescent Psychiatry 1162.

¹²⁹ “How Can Medication Help?” online: eHealthMD <<http://www.ehealthmd.com>>.

prescribed to children and adolescents off-label as treatment for depression and anxiety, yet there have still been no long-term clinical studies which demonstrate that these drugs are safe for use in children and adolescents. Consequently, it is frightening that there does not appear to be any real regulation of these medications for use in children and adolescents in Canada. It appears that all of the actors involved: the drug manufacturers, Health Canada, professional associations like CPA and CACAP, and physicians, are failing children and adolescents. Until there is more concrete and independently verified research that demonstrates the short-term and long-term consequences of SSRI use in children and adolescents, physicians should err on the side of caution and simply not prescribe these medications to children and young adolescents. While SSRIs can undoubtedly be “miracle drugs” for some older adolescents, the risk to the vast majority of others does not outweigh the benefits. Unfortunately, for many, the cure is worse than the disease.