BMJ Paediatrics Open

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Journal:	*BMJ Paediatrics Open*
Manuscript ID	bmjpo-2020-000674
Article Type:	Original research
Date Submitted by the Author:	05-Mar-2020
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Keywords:	Alternative Medicine

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Study Of Natural products Adverse Reactions (SONAR) in children seen in mental health clinics - a cross sectional study

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Acknowledgment:
We would like to thank to all members of the SONAR steering committee for their contributions on the development of the SONAR projects. A special thank you to Dr. Heather Boon for her ongoing active collaboration in this work.

Key words: natural health products, adverse events, mental health, pediatrics

Abstract

Background: Pediatric mental health patients frequently use natural health products (NHP) in addition to prescription medications, but very little is known about adverse events and possible NHP-drug interactions.

Objective: to determine: 1) the prevalence of pediatric mental health patients taking prescription medications only, NHP only, both NHP, and prescription medications concurrently or neither; 2) which prescription medications and NHP are most commonly used in pediatric mental health populations; 3) adverse events experienced in the last 30 days (serious and non-serious).

Design: Cross sectional surveillance study.

Setting: Pediatric mental health clinics.

Population/Intervention: On their first clinic visit, pediatric mental health patients were provided with a form inquiring about prescription drug use, NHP use, and any undesirable event experienced in the last month.

Results: Of the 536 patients included in this study, 23% (N=120) reported taking only prescription medication(s), 21% (N=109) reported only NHP use, 21% (N=112) reported using both NHP and prescription drugs concurrently, and 36% (N=191) reported using neither. Overall, there were 23 adverse event reported; this represents 6.3%, 2.8%, 10.8%, and 0.6% of each population, respectively. The majority of patients who experienced an adverse event reported taking more than one NHP or prescription drug. No serious adverse events were reported.

Conclusion: Nearly half of the pediatric mental health patients in this study were taking NHPs alone or in addition to prescription medications. Active surveillance identified multiple adverse events associated with NHP and prescription drug use; none were serious. Healthcare professionals were encouraged to initiate conversations regarding NHP use.

What is known:

- Pediatric mental health conditions are highly prevalent worldwide.
- Patients with chronic conditions often use natural health products.
- Polypharmacy use increased the number to adverse events experienced by the patient.
- Active surveillance of adverse events is more reliable method of pharmacovigilance if compared to passive methods.

What this study adds:

- Children with mental health conditions take natural health products in addition to prescription medications.
- Active surveillance demonstrated to be feasible in the clinical setting.

Introduction

Pediatric mental health conditions are highly prevalent worldwide. In Canada and United States it is estimated that between 15-25% of youth experience at least one mental health disorder[1,2]. In France, a cohort study found 6.3% of 17 year old girls were prescribed a psychotropic drugs (anxiolytic, antidepressant or hypnotic).[3] In Iceland, a population survey found that 4.9% of children and adolescents were in use of a psychotropic drug[4].

NHPs are commonly used in patients with serious, chronic or recurrent illness, including patients with mental health conditions[2]. A recent study found that 56.3% of pediatric patients with chronic health problems were taking NHPs in addition to conventional therapy [5]. Two adult cross sectional studies done in patients with mental health conditions found 25% to 66% of patients use at least one NHP and often in association with prescription drugs (29.7% to 58%)[6,7]. The high prevalence of NHP use in patients with mental health disorders may be attributed to factors like easier accessibility than prescription medications, dissatisfaction with conventional medications, and the perceived “naturalness” of NHPs[7,8]. Many patients assume that because a product is “natural”, it

is safe, and will have fewer side effects [9]. In Canada, NHP are regulated by Health Canada and include vitamins and minerals, herbal medicines, homeopathic remedies, traditional Chinese medicine, probiotics, amino acids and essential fatty acids[10]. NHPs used to support mental health include valerian, kava, ginko and St. John's wort, which interact with commonly used medications, [11,12]. For example, the use of selective serotonin reuptake inhibitors (SSRIs) with St John's wort could result in serotonin syndrome [13].

The risk of interactions and adverse events increases with the number of products taken[14]. In a population survey, the incidence of potentially serious drug-drug interaction was directly associated with the number of drugs dispensed: 10.9% if dispensed 2-4 drugs vs. 80.8% if dispensed ≥ 15 drugs[15]. Recently it was found that adult patients with mental health disorders taking prescription and NHP concurrently are 2.8 times more likely to experience an adverse event than patients taking prescription medications alone[16]. To date there are no data on the risk of NHP- drug interactions and adverse events among children with mental health disorders.

We undertook a cross-sectional surveillance study to investigate the adverse events associated with concurrent NHP and prescription drug use in pediatric mental health patients. The objectives of this study were to determine: 1) the prevalence of pediatric mental health patients taking prescription medications only, NHPs only, NHPs and prescription medications concurrently, or neither; 2) which prescription medications and NHPs are most commonly used in pediatric mental health populations; and 3) adverse events experienced in the last 30 days (serious and non-serious).

Methods

Approval by the Human Research and Ethics Board at the University of Alberta was granted for this study. We followed the STROBE guideline to report this observational study [17]. Patients and the public were not involved in the development of methods, analysis or dissemination of this study.

Eight pediatric mental health clinics in Alberta were invited to participate in this project. Each clinic was provided with initial on-site training in the relevance of the projects and how to use the screening forms, in addition, follow-up meetings and ongoing phone, email and on site contact were provided by the research group throughout the study period to support clinics and answer

any possible questions. All required resources, digital and hard copy screening logs for printing and distribution, training presentations, and definitions of NHP and drugs were provided to participating clinics.

NHPs are defined by Health Canada as a substance which includes vitamins and minerals, herbal medicines, homeopathic remedies, traditional medicines (e.g., traditional Chinese medicine), probiotics, amino acids and essential fatty acids as at least one of its medicinal ingredients[10]. We followed Health Canada's classification for an NHP, whether or not the NHP was prescribed. For example, oral iron supplementation was classified as a NHP as this is how it is classified by Health Canada, whether or not it was prescribed by a health professional[10].

A prescription drug was defined as any drug prescribed by a healthcare professional or an over-the-counter (OTC) drug with a drug identification number (D.I.N).

Adverse event was defined as an unexpected or undesirable event, including reduced or lack of therapeutic effect [16,18].

A serious adverse was defined as one that is: life-threatening, leads to initial or prolonged hospitalization, leads to persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, results in congenital anomaly/birth defect, causes death or an Important Medical Event (IME) that could be considered serious when, based on medical judgment, may jeopardize the patient or require medical or surgical intervention[19].

All patients/guardians of children up to 18 years old, receiving care from participating clinics were given a survey form on their first clinic visit, containing the following questions regarding their child's prescription drug use, NHP use, and adverse events in the last month.

Q1) In the last one month, has your child taken any prescription medications? *If **Yes**, list the medications and for how long have they been taken?*

Q2) In the last month, has your child taken any natural health products e.g. vitamins, minerals, herbals, homeopathic remedies, traditional Chinese medicines, probiotics etc.? *If **Yes**, list the natural health products and for how long have they been taken.*

Q3A) In the last 1 month, has your child experienced any unexpected or undesirable effects? *If **Yes**, describe the effects.*

Q3B) *What did you do about it?*

(*i)nothing, (ii) treated myself, (iii) phoned for information, (iv) saw a doctor about it, (v) doctor ordered tests, (vi) doctor treated it or (vii) my child was hospitalized*

The completed form was reviewed by the patient's clinic health care professional (therapist, nurse, physician, etc.), who would assess any adverse event reported by the patient and identify if, in their opinion, the event was 'serious'; 'unexpected' and/or 'caused a delay or change in treatment'. The patient's healthcare professional was also given the opportunity to report any other adverse event by answering the question:

> **Q4)** In the last month, has the patient had any other adverse events? *If **Yes**, describe the event and investigation/treatment required.* **Please identify if:** Serious, unexpected or caused a delay or change in treatment.

These screening questions were considered part of 'Best Possible Medication History (BPMH), as suggested by the Canadian Institute of Patient Safety, meaning that a systematic approach to interview patient or family should be undertaken in every clinic visit as part of best practice[20].

In this study, adverse event seriousness was identified based on: (i) event reported, (ii) the level of care sought by the participant to treat the adverse event and (iii) the health care provider assessment of the event (if considered the event serious or not). If a potential serious adverse event was identified, the patient/guardian was asked if they would like to participate in a research study to learn more about the adverse event. If the patient or guardian consented, the study coordinator contacted the patient within one week. Via a phone interview, our team obtained verbal consent, and inquired about the patient's health state and all products (prescription, OTC and NHPs) including brand and dose. If appropriate, we requested permission to obtain samples of the products via courier; these samples would then be shipped directly to participating laboratories for analysis of possible contaminants or adulterants. If a serious adverse event associated with a NHP occurred, it would be forwarded to Health Canada within 48 hours of identification for their review.

Data collection and data analysis

Study data were collected and managed using REDCap (Research Electronic Data Capture) tools hosted at University of Alberta[2,21].

Proportions were calculated using Stata version 14.0 [22]. Weighted proportions with their associated 95% confidence interval (CI) were calculated for proportions of use in each category (prescription drug only use, NHP only use, concurrent use and neither), as well as their respective adverse event proportions using logistic regression models. The odds ratios and 95% CI was

estimated using a logistic regression model for patients using concurrent NHP-prescription drugs compared with prescription drugs only. Microsoft Excel was used to perform the descriptive analysis (multiple response analysis and frequency analysis) for the commonly used prescription drugs, NHPs and adverse events.

Results

Five mental health clinics participated in the study. A total of 539 patients was each screened once between 2014 to June 2018. Seven incomplete surveys were excluded from analysis (one did not provide information about prescription drug use; one did not provide information about NHP use; four had unspecified locations and therefore could not be weighted appropriately; one reported an adverse event, but did not report if patient was taking NHP or prescription drugs). Of the 532 included patients, 229 reported diagnostic information with the most common being anxiety (N=83) and ADHD (N=77). More detailed information about the study population can be found in Table 1.

Adverse Events

A total of 492 of 532 (92.5%) forms provided complete adverse event information to be included in the analysis. Overall, 4.7% (N=23) of patients with complete adverse event data reported an adverse event. More details on the adverse events reported in each category are found in Figure 1. Table 2 provides more details of all 23 adverse events identified.
The number of adverse events increased proportionally with the number of products taken (Figure 2). Of the patients taking 3 prescription medications, 28.6% experienced an adverse event. More than 70% of patients who experienced an adverse event were taking more than one product (NHP or drug).

The adverse events reported ranged from feeling unusual, to suicidal ideation, however the most common adverse event were fatigue (18.3%) and decreased appetite (18.3%). No serious adverse events were reported. One patient reported suicidal ideation was not taking any NHP or prescription drugs, s/he was not hospitalized and the health care professional did not identify the event as serious, therefore it did not fulfill the study criteria for seriousness.

The odds ratio (OR) for adverse events for patients taking both NHP/prescription drugs vs. NHPs only is 4.24 (1.16-15.48, p=0.03).

The most common prescription medications taken were methylphenidate (N=32) and oral contraception (birth control pill) (N=24). The most common NHPs were multivitamins (N=101) and melatonin (N=82). The most common NHP-drug combinations taken were methylphenidate and melatonin (N=11) and methylphenidate and multivitamins (N=10).

Discussion

Mental health conditions are highly prevalent and generate a high health care cost, in United States for example, it is estimated at 247 billion dollars per year[1,23]. Parents and patients often seek alternatives to prescription medications for management of mental health conditions. Many children and parents opt to use complementary therapies as adjunct treatment for mental health conditions because they are perceived as helpful and natural[7]. Despite the frequency of NHP use in pediatric mental health conditions, there are no studies to our knowledge assessing NHP-drug related adverse events in this population.

We present the first cross sectional active surveillance study of adverse events associated with NHP and prescription drug use in pediatric patients with mental health conditions. Nearly half of patients included in the study were taking NHPs, alone or in association with a prescription medication. A majority of adverse events identified was associated with the use of two or more products. Necyk et al. found that 25.5% of adult mental health patients taking NHPs and drugs concurrently experienced an adverse event [16], however, adult mental health patients are more likely to be taking a higher dose and quantity of medications than pediatric patients, which increases the chances of adverse events[24].

Polypharmacy is well known to increase the risk of adverse events in multiple populations. In a population based study in Scotland over 15 years, the proportion of adults dispensed ≥5 drugs doubled, as a consequence the proportion of potentially serious drug-drug interactions more than doubled in the same period[15]. Older outpatient adults taking 5 or more medications had an 88% increased risk of experiencing an adverse drug event compared to those who were taking fewer medications[25]. Interaction was also a concern: in hospitalized adults taking 5 or more

medications, the prevalence of a potential hepatic cytochrome enzyme-mediated drug-drug interaction was 80%[26]. NHP and prescription drugs are often used in combination in children, but multiple studies have confirmed that NHP use is often not disclosed to the health care professional [27,28].

Adults with mental health conditions are known to have high intake of NHP [16,29]. In a study by Necyk et al., 19% of adult mental health patients reported using NHPs and prescription medications concurrently [16]. We found a similar rate of concurrent use, suggesting that pediatric patients frequently take NHPs in association with prescription medications. The results of our study were consistent with similar studies involving concurrent drug and NHP use in mental health patients [5,7,16,30]. In a recent study, Wang identified that American children with mental health disorders are more commonly using complementary treatments compared to those without (19.2% compared to 10.1%,p<0.001) and herbal medicines are the most frequently used modality[31].

Study Strengths

This study uses active surveillance to investigate NHP and drug adverse events s in pediatric mental health patients. Active surveillance "seeks to ascertain completely the number of adverse events via a continuous pre-organized process" which appears to increase rates of reporting, produce better quality reports and encourage communication between patients and healthcare professionals regarding NHPs [9]. Active surveillance has been used in the past to investigate NHP-drug adverse events; however to our knowledge, this is the first study to investigate in this population. Most countries, including Canada, use passive surveillance in detecting adverse events, which refers to voluntary reporting of an adverse event[32]. Although passive surveillance has the capacity to identify rare adverse events, underreporting and poor quality reports make this method less than ideal [9] In a study by Zimmerman et al., active surveillance identified 1.65 adverse events reports per every 100 pediatric patients, compared to the Canada Vigilance Program which used passive surveillance and only identified 0.17 adverse events in every 100 pediatric patients. [33] Our active surveillance study identified 4.5 adverse events per 100 pediatric patients with mental health conditions. Active surveillance has been found to increase adverse event reporting and we have demonstrated its feasibility in the clinical setting[16].

This study identified that pediatric mental health patients are often using NHPs, with nearly half of included patients reporting NHP use. The Canadian Safety Institute recommends, as part of best possible medication history, that all product history should be obtained at every clinic visit; however, in practice NHP use and adverse event reporting are rarely captured [16] Patients have reported that they believe that NHPs are 'natural' and therefore safe, suggesting that patients believe that healthcare professionals do not need to know about such use [9]. In a study by Adams et al., only 20% of pediatric patients told either their physician or pharmacist that they were using complementary therapies concurrently with prescription medication [5]. Without adequate reporting, the safety of pediatric NHP use is uncertain[34]. Our study stimulated discussion between patients and health care providers about NHP use. Discussing all therapies and their reasons for use promotes patient-centred care as well as patient safety. We hope this practice will remain after the study ends, as part of best practice.

Study Weaknesses

A possible limitation of our study is that NHP/drug use and corresponding adverse events were sought during the first clinic visit. While this simplifies analysis by ensuring data are independent, we feel patients should be asked about all products and all adverse events at every visit.

Additionally, this study was limited to five mental health clinics within one geographical area (Alberta, Canada). Thus, our study may not represent NHP use in other settings; further work to investigate NHP use by pediatric mental health patients in different settings is needed and encouraged.

This study identified reported adverse events and possible association with prescription drugs and NHP, although direct causation of the adverse event was not investigated. While we had study methods to allow for more definitive assessment of adverse event, such as laboratory assessment, these resource-intensive methods were reserved for serious adverse event, which did not occur.

Future Steps

Best possible medication history (BPMH) advocates for collection of accurate information of all therapies taken by the patient, which should include prescription drugs and NHPs[20]. There is also a need to expand the BPMH inquires to include any possible undesirable adverse effects caused by therapeutic products, increasing awareness of possible adverse effects to patients and health care professionals. Product-related adverse effects are responsible for multiple hospital admissions and the morbidity and mortality related the adverse events is directly associated to the number of drugs taken[35,36]. Open discussion between patients and healthcare professionals regarding all therapies, including NHPs, and associated adverse events are key to fully understanding patient's health. Promoting the discussion of NHP use is critical to to enhance patient safety and promote patient-centered care[37].

Pharmacoepidemiological surveillance is a key element to improve patient safety outcomes. Adverse events are often rare. Information on AEs acquired on population level are feasible and reliable method to identity adverse events, or lack thereof, which is also informative.
Any surveillance study does not have a primary goal to improve clinical outcomes. Surveillance studies identify safety signals. Once a signal is identified, it triggers further investigation to assess its definitive causality and clinical practice change as a further step. If adverse events are not monitored, they are often not reported and neglected, but still present, ultimately injuring patients due its lack of investigation.

The probability of identifying and reporting an adverse event increases dramatically when using active surveillance [33]. This study introduced active surveillance as a mechanism to help clinical staff become comfortable asking about NHP use, and shown itself to be feasible. The study has ended, but it appears participating health care professionals have incorporated questions about NHP use and product-related adverse events as part of their routine patient history.

Continued research into the concurrent use of NHPs and prescription medications support the development of a database of which combinations have associated adverse effects and which do not, greatly enhancing current knowledge of clinically relevant NHP-drug interactions.

Conclusion

In this observational study of adverse events in pediatric mental health patients, many patients were taking NHPs, alone or in combination with a prescription medication. Polypharmacy, including mixing NHPs and prescription medications, increases the likelihood of an adverse events; no serious adverse events were identified in this study. Active surveillance has demonstrated it is feasible and should be considered as a preferred method of pharmacovigilance to enhance adverse event identification and reporting.

This work was supported by a partnered grant form Canadian Institute of Health Research (CIHR) (#RES0021177) and Alberta Innovates Health Solutions (AIHS) (#RES0025318).

The authors have no competing interests to declare.

ES, LZ, BK and CN collected and analyzed the data. JB, LU and SV developed the idea. LZ, BK, CN, JB, LU, SV implemented the project. ES, LZ, BK, CN, JB, LU, SV developed the manuscript and revised the final version submitted.

The authors agree in sharing the data upon request.

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Table 1. Characteristics of study population

		Number of Patients (539)
Gender	Male	236 (44%)
	Female	277 (51%)
	Not Filled	26 (5%)
Age (years)*	0-3	0 (0%)
	4-7	67 (12%)
	8-11	93 (17%)
	12-15	143 (27%)
	16-18	62 (12%)
	Not Filled	173 (32%)
Diagnosis/Disorder (most frequently reported)	Not Filled	313 (58%)
	Anxiety**	84 (15%)
	Attention deficit hyperactivity disorder (ADHD)	77 (14%)
	Depression	33 (6%)
	Oppositional defiant disorder (ODD)	22 (4%)
	Other	16 (3%)

Age in years at time of form completions

Anxiety*= includes all types of anxiety: social anxiety (N=7), separation anxiety (N=2) and general anxiety (N=75)

Figure 1: NHP and prescription drugs use and related AEs

Table 2. Summary information for reported AEs for patients taking Rx meds and/or NHPs

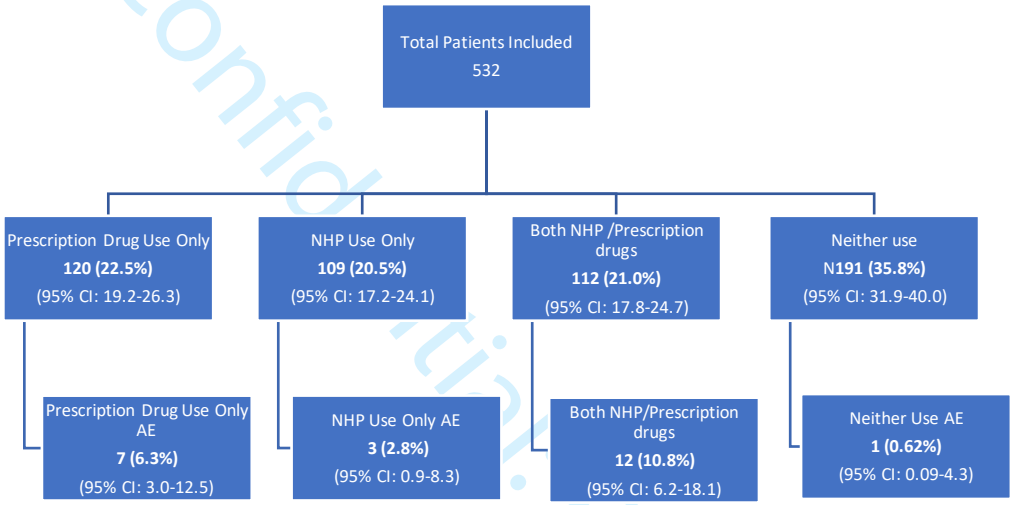
	Patient ID	Age	Gender	Diagnosis	Drug	NHP	AE
Drugs only	P1	ns	male	chronic pain	tramadol, cyclobenzaprine and diclofenac		fatigue
	P2	16	male	ns	metformin, sertraline and insulin		unusual feeling
	P3	14	male	ADHD, FASD, intellectual disability	methylphenidate and trazodone		breathing problems
	P4	16	female	ns	aripiprazole		fatigue
	P5	8	male	ns	citalopram		upset stomach
	P6	5	female	ADHD	lisdexamfetamine		shaking
	P7	11	male	ADHD and ODD	Methylphenidate, fluvoxamine and methylphenidate		poor sleep
	P8	9	male	ADHD	methylphenidate		decreased appetite
	P9	ns	female	ns	polyethylene glycol, risperidone and methylphenidate		decreased appetite
NHP only	P10	ns	female	ns		multivitamin and melatonin	felt woozy
	P11	14	female	anxiety		5-hydroxytryptophan (5-HTP)	adverse reaction not specified
	P12	9	male	ns		vitamin D	headaches

NHP and Drugs	P13	7	male	ADHD	lisdexamfetamine	multivitamin and omega 3	decreased appetite
	P14	16	female	ns	vortioxetine	vitamin D and multivitamin	headaches and dizzy
	P15	6	male	PTSD and anxiety	methylphenidate and trazodone	melatonin	increased anger and agitation
	P16	16	ns	epilepsy, spasticity, brain Injury, optic atrophy, cerebral palsy	levetiracetam, aripiprazole, carbamazepine, clobazam, lamotrigine and escitalopram oxalate	melatonin and multivitamin	fatigue
	P17	17	female	ns	norgestimate-ethinyl estradiol, itch oitment and topical lotion	chlorophyll	labile mood (mood swings)
	P18	15	female	ns	citalopram and desogestrel-ethinyl estradiol	vitamin B12	fatigue
	P19	10	male	ns	lisdexamfetamine	melatonin	decreased appetite
	P20	7	male	ADHD	methylphenidate and clonidine	multivitamin	migraines
	P21	ns	male	ADHD and query anxiety	guanfacine	melatonin	personality change
	P22	ns	Male	Bi-Polar	olanzapine, trazodone and lithium carbonate	multivitamin	thyroid condition developed

Neither	P23	ns	female	ns	gets violent when angry (yelling, hitting, wants to kill herself)

Figure 2: Percentage of patients experiencing an adverse event and number of products taken

Figure 1 :NHP and prescription drugs use and related AEs



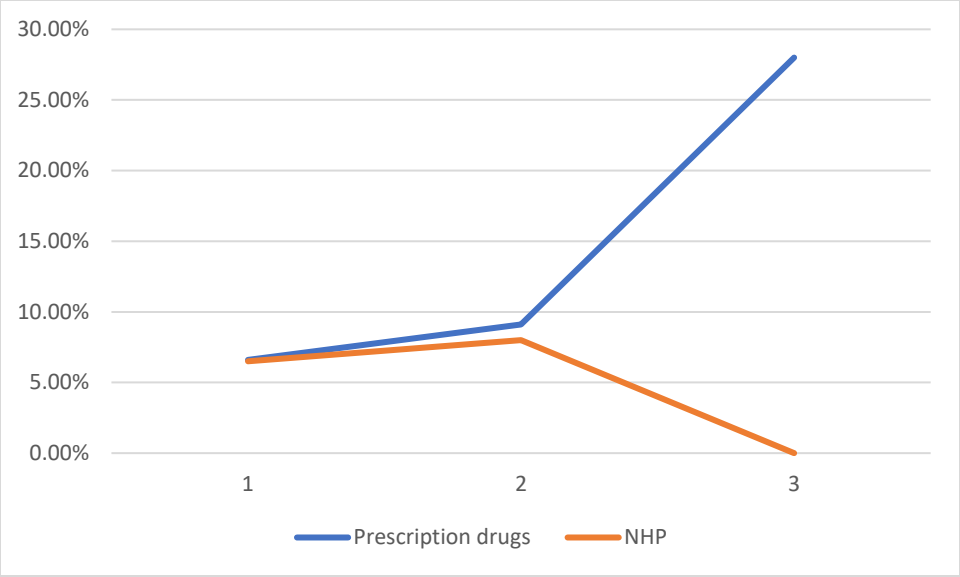


Figure 2: Percentage of patients experiencing an adverse event and number of products taken

BMJ Paediatrics Open

Study Of Natural products Adverse Reactions (SONAR) in children seen in mental health clinics - a cross sectional study

Journal:	*BMJ Paediatrics Open*
Manuscript ID	bmjpo-2020-000674.R1
Article Type:	Original research
Date Submitted by the Author:	01-Jun-2020
Complete List of Authors:	Sparks, Emma; Queen's University Faculty of Arts and Science Zorzela, Liliane; University of Alberta, Pediatrics Necyk, Candace ; University of Alberta, Pharmacy and Pharmaceutical Sciences Khamba, Baljit ; University of Alberta Urichuk, Liana ; University of Alberta, Physichiatry Barnes, Jo; University of Auckland School of Education, School of Pharmacy Vohra, Sunita; University of Alberta
Keywords:	Alternative Medicine

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Study Of Natural products Adverse Reactions (SONAR) in children seen in mental health clinics - a cross sectional study

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Acknowledgment:
We would like to thank to all members of the SONAR steering committee for their contributions on the development of the SONAR projects. A special thank you to Dr. Heather Boon for her ongoing active collaboration in this work.

Key words: natural health products, adverse events, mental health, pediatrics

Abstract

Background: Pediatric mental health patients frequently use natural health products (NHP) in addition to prescription medications, but very little is known about adverse events and possible NHP-drug interactions.

Objective: to determine: 1) the prevalence of pediatric mental health patients taking prescription medications only, NHP only, both NHP, and prescription medications concurrently or neither; 2) which prescription medications and NHP are most commonly used in pediatric mental health populations; 3) adverse events experienced in the last 30 days (serious and non-serious).

Design: Cross sectional surveillance study.

Setting: Pediatric mental health clinics.

Population/Intervention: On their first clinic visit, pediatric mental health patients were provided with a form inquiring about prescription drug use, NHP use, and any undesirable event experienced in the last month.

Results: Of the 536 patients included in this study, 23% (N=120) reported taking only prescription medication(s), 21% (N=109) reported only NHP use, 21% (N=112) reported using both NHP and prescription drugs concurrently, and 36% (N=191) reported using neither. Overall, there were 23 adverse event reported; this represents 6.3%, 2.8%, 10.8%, and 0.6% of each population, respectively. The majority of patients who experienced an adverse event reported taking more than one NHP or prescription drug. No serious adverse events were reported.

Conclusion: Nearly half of the pediatric mental health patients in this study were taking NHPs alone or in addition to prescription medications. Active surveillance identified multiple adverse events associated with NHP and prescription drug use; none were serious. Healthcare professionals were encouraged to initiate conversations regarding NHP use.

What is known:

- Pediatric mental health conditions are highly prevalent worldwide.
- Patients with chronic conditions often use natural health products.
- Polypharmacy use increased the number to adverse events experienced by the patient.
- Active surveillance of adverse events is more reliable method of pharmacovigilance if compared to passive methods.

What this study adds:

- Children with mental health conditions take natural health products in addition to prescription medications.
- Active surveillance demonstrated to be feasible in the clinical setting.

Introduction

Pediatric mental health conditions are highly prevalent worldwide. In Canada and United States it is estimated that between 15-25% of youth experience at least one mental health disorder[1,2]. In France, a cohort study found 6.3% of 17 year old girls were prescribed a psychotropic drugs (anxiolytic, antidepressant or hypnotic).[3] In Iceland, a population survey found that 4.9% of children and adolescents were in use of a psychotropic drug[4].

NHPs are commonly used in patients with serious, chronic or recurrent illness, including patients with mental health conditions[2]. A recent study found that 56.3% of pediatric patients with chronic health problems were taking NHPs in addition to conventional therapy [5]. Two adult cross sectional studies done in patients with mental health conditions found 25% to 66% of patients use at least one NHP and often in association with prescription drugs (29.7% to 58%)[6,7]. The high prevalence of NHP use in patients with mental health disorders may be attributed to factors like easier accessibility than prescription medications, dissatisfaction with conventional medications, and the perceived “naturalness” of NHPs[7,8]. Many patients assume that because a product is “natural”, it

is safe, and will have fewer side effects [9]. In Canada, NHP are regulated by Health Canada and include vitamins and minerals, herbal medicines, homeopathic remedies, traditional Chinese medicine, probiotics, amino acids and essential fatty acids[10]. NHPs used to support mental health include valerian, kava, ginko and St. John's wort, which interact with commonly used medications, [11,12]. For example, the use of selective serotonin reuptake inhibitors (SSRIs) with St John's wort could result in serotonin syndrome [13].

The risk of interactions and adverse events increases with the number of products taken[14]. In a population survey, the incidence of potentially serious drug-drug interaction was directly associated with the number of drugs dispensed: 10.9% if dispensed 2-4 drugs vs. 80.8% if dispensed ≥ 15 drugs[15]. Recently it was found that adult patients with mental health disorders taking prescription and NHP concurrently are 2.8 times more likely to experience an adverse event than patients taking prescription medications alone[16]. To date there are no data on the risk of NHP- drug interactions and adverse events among children with mental health disorders.

We undertook a cross-sectional surveillance study to investigate the adverse events associated with concurrent NHP and prescription drug use in pediatric mental health patients. The objectives of this study were to determine: 1) the prevalence of pediatric mental health patients taking prescription medications only, NHPs only, NHPs and prescription medications concurrently, or neither; 2) which prescription medications and NHPs are most commonly used in pediatric mental health populations; and 3) adverse events experienced in the last 30 days (serious and non-serious).

Methods

Approval by the Human Research and Ethics Board at the University of Alberta was granted for this study. We followed the STROBE guideline to report this observational study [17]. Patients and the public were not involved in the development of methods, analysis or dissemination of this study.

Eight pediatric mental health clinics in Alberta were invited to participate in this project. Each clinic was provided with initial on-site training in the relevance of the projects and how to use the screening forms, in addition, follow-up meetings and ongoing phone, email and on site contact were provided by the research group throughout the study period to support clinics and answer

any possible questions. All required resources, digital and hard copy screening logs for printing and distribution, training presentations, and definitions of NHP and drugs were provided to participating clinics.

NHPs are defined by Health Canada as a substance which includes vitamins and minerals, herbal medicines, homeopathic remedies, traditional medicines (e.g., traditional Chinese medicine), probiotics, amino acids and essential fatty acids as at least one of its medicinal ingredients[10]. We followed Health Canada's classification for an NHP, whether or not the NHP was prescribed. For example, oral iron supplementation was classified as a NHP as this is how it is classified by Health Canada, whether or not it was prescribed by a health professional[10].

A prescription drug was defined as any drug prescribed by a healthcare professional or an over-the-counter (OTC) drug with a drug identification number (D.I.N).

Adverse event was defined as an unexpected or undesirable event, including reduced or lack of therapeutic effect as assessed by clinical opinion [16,18].

A serious adverse event was defined as one that is: life-threatening, leads to initial or prolonged hospitalization, leads to persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, results in congenital anomaly/birth defect, causes death or an Important Medical Event (IME) that could be considered serious when, based on medical judgment, may jeopardize the patient or require medical or surgical intervention[19].

All patients/guardians of children up to 18 years old, receiving care from participating clinics were given a survey form on their first clinic visit, containing the following questions regarding their child's prescription drug use, NHP use, and adverse events in the last month.

Q1) In the last one month, has your child taken any prescription medications? *If **Yes**, list the medications and for how long have they been taken?*

Q2) In the last month, has your child taken any natural health products e.g. vitamins, minerals, herbals, homeopathic remedies, traditional Chinese medicines, probiotics etc.? *If **Yes**, list the natural health products and for how long have they been taken.*

Q3A) In the last 1 month, has your child experienced any unexpected or undesirableeffects? *If **Yes**, describe the effects.*

Q3B) *What did you do about it?*

(*i)nothing, (ii) treated myself, (iii) phoned for information, (iv) saw a doctor about it, (v) doctor ordered tests, (vi) doctor treated it or (vii) my child was hospitalized*

The completed form was reviewed by the patient's clinic health care professional (therapist, nurse, physician, etc.), who would assess any adverse event reported by the patient and identify if, in their opinion, the event was 'serious'; 'unexpected' and/or 'caused a delay or change in treatment'. The patient's healthcare professional was also given the opportunity to report any other adverse event by answering the question:

> **Q4)** In the last month, has the patient had any other adverse events? *If **Yes**, describe the event and investigation/treatment required.* **Please identify if:** Serious, unexpected or caused a delay or change in treatment.

These screening questions were considered part of 'Best Possible Medication History (BPMH), as suggested by the Canadian Institute of Patient Safety, meaning that a systematic approach to interview patient or family should be undertaken in every clinic visit as part of best practice[20].

In this study, adverse event seriousness was identified based on: (i) event reported, (ii) the level of care sought by the participant to treat the adverse event and (iii) the health care provider assessment of the event (if considered the event serious or not). If a potential serious adverse event was identified, the patient/guardian was asked if they would like to participate in a research study to learn more about the adverse event. If the patient or guardian consented, the study coordinator contacted the patient within one week. Via a phone interview, our team obtained verbal consent, and inquired about the patient's health state and all products (prescription, OTC and NHPs) including brand and dose. If appropriate, we requested permission to obtain samples of the products via courier; these samples would then be shipped directly to participating laboratories for analysis of possible contaminants or adulterants. If a serious adverse event associated with a NHP occurred, it would be forwarded to Health Canada within 48 hours of identification for their review.

Data collection and data analysis

Study data were collected and managed using REDCap (Research Electronic Data Capture) tools hosted at University of Alberta[2,21].

Results

Five mental health clinics participated in the study. A total of 539 patients was each screened once between 2014 to June 2018. Seven incomplete surveys were excluded from analysis (one

did not provide information about prescription drug use; one did not provide information about NHP use; four had unspecified locations and therefore could not be weighted appropriately; one reported an adverse event, but did not report if patient was taking NHP or prescription drugs). Of the 532 included patients, 229 reported diagnostic information with the most common being anxiety (N=83) and ADHD (N=77). More detailed information about the study population can be found in Table 1.

Adverse Events

A total of 492 of 532 (92.5%) forms provided complete adverse event information to be included in the analysis. Overall, 4.7% (N=23) of patients with complete adverse event data reported an adverse event. More details on the adverse events reported in each category are found in Figure 1. Table 2 provides more details of all 23 adverse events identified.
The number of adverse events increased proportionally with the number of products taken Of the patients taking 3 prescription medications, 28.6% experienced an adverse event. More than 70% of patients who experienced an adverse event were taking more than one product (NHP or drug).

The adverse events reported ranged from migraines, to suicidal ideation, however the most common adverse event were fatigue (18.3%) and decreased appetite (18.3%). No serious adverse events were reported. One patient reported suicidal ideation was not taking any NHP or prescription drugs, s/he was not hospitalized and the health care professional did not identify the event as serious, therefore it did not fulfill the study criteria for seriousness.

The most common prescription medications taken were methylphenidate (N=32) and oral contraception (birth control pill) (N=24). The most common NHPs were multivitamins (N=101) and melatonin (N=82). The most common NHP-drug combinations taken were methylphenidate and melatonin (N=11) and methylphenidate and multivitamins (N=10).

Discussion

Mental health conditions are highly prevalent and generate a high health care cost, in United States for example, it is estimated at 247 billion dollars per year[1,22]. Parents and patients often

seek alternatives to prescription medications for management of mental health conditions. Many children and parents opt to use complementary therapies as adjunct treatment for mental health conditions because they are perceived as helpful and natural[7]. Despite the frequency of NHP use in pediatric mental health conditions, there are no studies to our knowledge assessing NHP-drug related adverse events in this population.

We present a cross sectional active surveillance study of adverse events associated with NHP and prescription drug use in pediatric patients with mental health conditions. Nearly half of patients included in the study were taking NHPs, alone or in association with a prescription medication. A majority of adverse events identified was associated with the use of two or more products. Necyk et al. found that 25.5% of adult mental health patients taking NHPs and drugs concurrently experienced an adverse event [16], however, adult mental health patients are more likely to be taking a higher dose and quantity of medications than pediatric patients, which increases the chances of adverse events[23].

Polypharmacy is well known to increase the risk of adverse events in multiple populations. In a population based study in Scotland over 15 years, the proportion of adults dispensed ≥5 drugs doubled, as a consequence the proportion of potentially serious drug-drug interactions more than doubled in the same period[15]. Older outpatient adults taking 5 or more medications had an 88% increased risk of experiencing an adverse drug event compared to those who were taking fewer medications[24]. Interaction was also a concern: in hospitalized adults taking 5 or more medications, the prevalence of a potential hepatic cytochrome enzyme-mediated drug-drug interaction was 80%[25]. NHP and prescription drugs are often used in combination in children, but multiple studies have confirmed that NHP use is often not disclosed to the health care professional [26,27].

Adults with mental health conditions are known to have high intake of NHP [16,28]. In a study by Necyk et al., 19% of adult mental health patients reported using NHPs and prescription medications concurrently [16]. We found a similar rate of concurrent use, suggesting that pediatric patients frequently take NHPs in association with prescription medications. The results of our study were consistent with similar studies involving concurrent drug and NHP use in mental health patients [5,7,16,29]. In a recent study, Wang identified that American children with mental health disorders are more commonly using complementary treatments compared to those without

(19.2% compared to 10.1%,p<0.001) and herbal medicines are the most frequently used modality[30].

Study Strengths

This study uses active surveillance to investigate NHP and drug adverse events in pediatric mental health patients. Active surveillance "seeks to ascertain completely the number of adverse events via a continuous pre-organized process" which appears to increase rates of reporting, produce better quality reports and encourage communication between patients and healthcare professionals regarding NHPs [9]. Active surveillance has been used in the past to investigate NHP-drug adverse events; however to our knowledge, this is the first study to investigate in this population. Most countries, including Canada, use passive surveillance in detecting adverse events, which refers to voluntary reporting of an adverse event[31]. Although passive surveillance has the capacity to identify rare adverse events, underreporting and poor quality reports make this method less than ideal [9] In a study by Zimmerman et al., active surveillance identified 1.65 adverse events reports per every 100 pediatric patients, compared to the Canada Vigilance Program which used passive surveillance and only identified 0.17 adverse events in every 100 pediatric patients. [32] Our active surveillance study identified 4.5 adverse events per 100 pediatric patients with mental health conditions. Active surveillance has been found to increase adverse event reporting and we have demonstrated its feasibility in the clinical setting[16].

This study identified that pediatric mental health patients are often using NHPs, with nearly half of included patients reporting NHP use. The Canadian Safety Institute recommends, as part of best possible medication history, that all product history should be obtained at every clinic visit; however, in practice NHP use and adverse event reporting are rarely captured [16] Patients have reported that they believe that NHPs are 'natural' and therefore safe, suggesting that patients believe that healthcare professionals do not need to know about such use [9]. In a study by Adams et al., only 20% of pediatric patients told either their physician or pharmacist that they were using complementary therapies concurrently with prescription medication [5]. To compound this issue, when patients do tell healthcare professionals about NHP AEs, many do not report that AE to Health Canada. In one study by Charrois et al, only 1.5% of pharmacists reported NHP-drug interactions to Health Canada[9]. Without adequate reporting, the safety of pediatric NHP use is

uncertain[33]. Our study stimulated discussion between patients and health care providers about NHP use and encouraged AE reporting through active surveillance. Discussing all therapies and their reasons for use promotes patient-centred care as well as patient safety. We hope this practice will remain after the study ends, as part of best practice.

Study Weaknesses

A possible limitation of our study is that NHP/drug use and corresponding adverse events were sought during the first clinic visit. While this simplifies analysis by ensuring data are independent, we feel patients should be asked about all products and all adverse events at every visit.

Additionally, this study was limited to five mental health clinics within one geographical area (Alberta, Canada). Thus, our study may not represent NHP use in other settings; further work to investigate NHP use by pediatric mental health patients in different settings is needed and encouraged.

This study identified reported adverse events and possible association with prescription drugs and NHP, although direct causation of the adverse event was not investigated. We are unable to differentiate whether patients with more symptoms take more medications, or if they take more medications and have more symptoms. While we had study methods to allow for more definitive assessment of adverse event, such as laboratory assessment, these resource-intensive methods were reserved for serious adverse event, which did not occur.

Future Steps

Best possible medication history (BPMH) advocates for collection of accurate information of all therapies taken by the patient, which should include prescription drugs and NHPs[20]. There is also a need to expand the BPMH inquires to include any possible undesirable adverse effects caused by therapeutic products, increasing awareness of possible adverse effects to patients and health care professionals. Product-related adverse effects are responsible for multiple hospital admissions and the morbidity and mortality related the adverse events is directly associated to the number of drugs taken[34,35]. Open discussion between patients and healthcare professionals

regarding all therapies, including NHPs, and associated adverse events are key to fully understanding patient's health. Promoting the discussion of NHP use is critical to to enhance patient safety and promote patient-centered care[36].

Pharmacoepidemiological surveillance is a key element to improve patient safety outcomes. Adverse events are often rare. Information on AEs acquired on population level are feasible and reliable method to identity adverse events, or lack thereof, which is also informative.
Any surveillance study does not have a primary goal to improve clinical outcomes. Surveillance studies identify safety signals. Once a signal is identified, it triggers further investigation to assess its definitive causality and clinical practice change as a further step. If adverse events are not monitored, they are often not reported and neglected, but still present, ultimately injuring patients due its lack of investigation.

The probability of identifying and reporting an adverse event increases dramatically when using active surveillance [32]. This study introduced active surveillance as a mechanism to help clinical staff become comfortable asking about NHP use, and shown itself to be feasible. The study has ended, but it appears participating health care professionals have incorporated questions about NHP use and product-related adverse events as part of their routine patient history.

Continued research into the concurrent use of NHPs and prescription medications support the development of a database of which combinations have associated adverse effects and which do not, greatly enhancing current knowledge of clinically relevant NHP-drug interactions.

Conclusion

In this observational study of adverse events in pediatric mental health patients, many patients were taking NHPs, alone or in combination with a prescription medication. Polypharmacy, including mixing NHPs and prescription medications, increases the likelihood of an adverse events; no serious adverse events were identified in this study. Active surveillance has demonstrated it is feasible and should be considered as a preferred method of pharmacovigilance to enhance adverse event identification and reporting.

This work was supported by a partnered grant form Canadian Institute of Health Research (CIHR) (#RES0021177) and Alberta Innovates Health Solutions (AIHS) (#RES0025318).

The authors have no competing interests to declare.

ES, LZ, BK and CN collected and analyzed the data. JB, LU and SV developed the idea. LZ, BK, CN, JB, LU, SV implemented the project. ES, LZ, BK, CN, JB, LU, SV developed the manuscript and revised the final version submitted.

The authors agree in sharing the data upon request.

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Table 1. Characteristics of study population

		Number of Patients (539)
Gender	Male	236 (44%)
	Female	277 (51%)
	Not Filled	26 (5%)
Age (years)*	0-3	0 (0%)
	4-7	67 (12%)
	8-11	93 (17%)
	12-15	143 (27%)

	16-18	62 (12%)
	Not Filled	173 (32%)
Diagnosis/Disorder (most frequently reported)	Not Filled	313 (58%)
	Anxiety**	84 (15%)
	Attention deficit hyperactivity disorder (ADHD)	77 (14%)
	Depression	33 (6%)
	Oppositional defiant disorder (ODD)	22 (4%)
	Other	16 (3%)

Age in years at time of form completions

Anxiety*= includes all types of anxiety: social anxiety (N=7), separation anxiety (N=2) and general anxiety (N=75)

Figure 1: NHP and prescription drugs use and related AEs

Table 2. Summary information for reported AEs for patients taking Rx meds and/or NHPs

	Drug	NHP	AE
Drugs only	tramadol, cyclobenzaprine and diclofenac		fatigue
	metformin, sertraline and insulin		unusual feeling
	methylphenidate and trazodone		breathing problems
	aripiprazole		fatigue

	citalopram		upset stomach
	lisdexamfetamine		shaking
	Methylphenidate, fluvoxamine and methylphenidate		poor sleep
	methylphenidate		decreased appetite
	polyethylene glycol, risperidone and methylphenidate		decreased appetite
NHP only		multivitamin and melatonin	felt woozy
		5-hydroxytryptophan (5-HTP)	adverse reaction not specified
		vitamin D	headaches
NHP and Drugs	lisdexamfetamine	multivitamin and omega 3	decreased appetite
	vortioxetine	vitamin D and multivitamin	headaches and dizzy
	methylphenidate and trazodone	melatonin	increased anger and agitation
	levetiracetam, aripiprazole, carbamazepine, clobazam, lamotrigine and escitalopram oxalate	melatonin and multivitamin	fatigue

	norgestimate-ethinyl estradiol, itch oitment and topical lotion	chlorophyll	labile mood (mood swings)
	citalopram and desogestrel-ethinyl estradiol	vitamin B12	fatigue
	lisdexamfetamine	melatonin	decreased appetite
	methylphenidate and clonidine	multivitamin	migraines
	guanfacine	melatonin	personality change
	olanzapine, trazodone and lithium carbonate	multivitamin	thyroid condition developed
Neither			gets violent when angry (yelling, hitting, wants to kill herself)

Figure 1: NHP and prescription drugs use and related AEs