ACTIVE EMERGENCE FROM ISOFLURANE GENERAL ANESTHESIA INDUCED BY METHYLPHENIDATE

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I. INTRODUCTION AND BACKGROUND

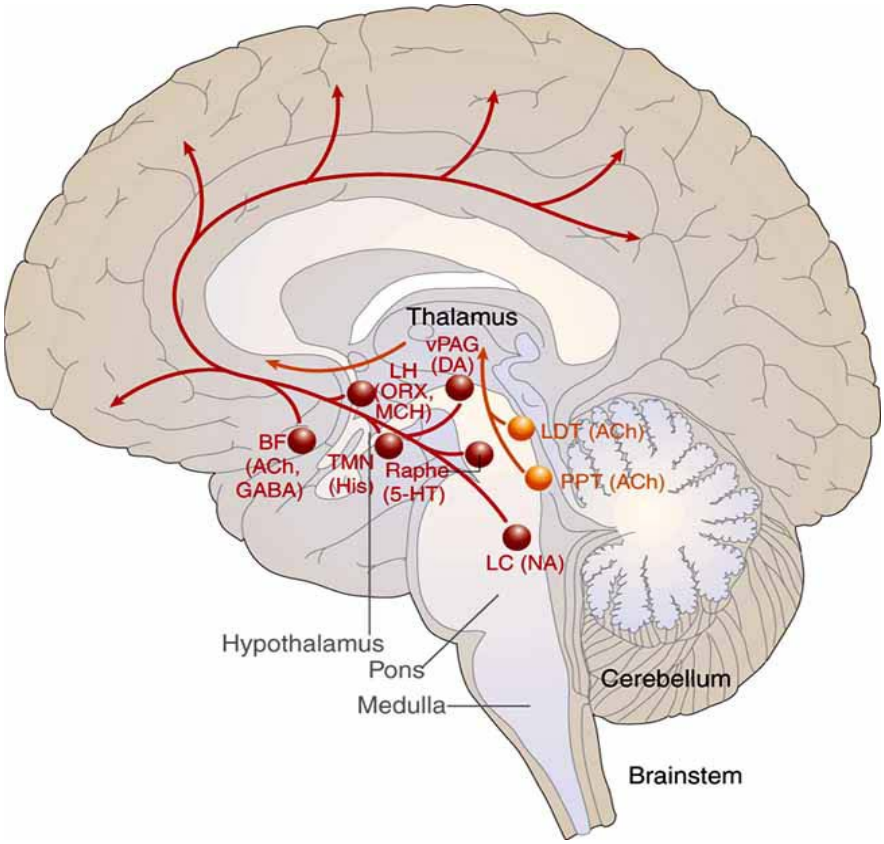
General anesthesia (GA) is the induction of a balanced state of unconsciousness, accompanied by the absence of pain sensation and the paralysis of skeletal muscles throughout the body. It is induced through the administration of anesthetic drugs and is used during major surgery and other invasive surgical procedures (1).

The precise mechanism of general anesthesia is not yet fully understood. There are, however, several hypotheses that have been advanced to explain why general anesthesia occurs. The Meyer-Overton theory suggests that anesthesia occurs when a sufficient number of molecules of an inhalation anesthetic dissolve in the lipid cell membrane. Linus Pauling, in 1961, suggested that anesthetic molecules interact with water molecules to form clathrates (hydrated microcrystals), which in turn inhibit receptor function (2).

The defining characteristic of general anesthetics is the ability to produce a reversible loss of consciousness. Although the molecular targets of many anesthetics have been identified, they are widely distributed in the central nervous system. Therefore, identifying the locus of action of these drugs in the brain represents a major challenge. The neuronal mechanisms of sleep, a physiologic state that involves a loss of consciousness, provide one obvious avenue of enquiry (1). Brain imaging and electroencephalographic studies give a broad characterization of the anesthetic state and show clear similarities with the sleeping brain. However, natural sleep and wakefulness are controlled by multiple arousal pathways, as well as by the intimate connectivity between the thalamus and the cortex.

Contemporary models of the wake-sleep regulatory system are based on the seminal research conducted by both von Economo and the team of Giuseppe Moruzzi and H.W. Magoun. (3). In 1930, von Economo reported that a viral illness known as encephalitis lethargica, or “sleepy sickness,” was caused by lesions of the posterior hypothalamus and rostral midbrain (4). He hypothesized that wakefulness is mediated by an ascending arousal system beginning in the brainstem, which remains active following midbrain interruption of the classical sensory pathways. Two decades later, Moruzzi, Magoun, and colleagues confirmed that waking

behavior is maintained by an "ascending reticular activating system," originating in the upper brainstem adjacent to the junction of the pons and midbrain and continuing on to the diencephalon, where it separates into two branches (5,6). In fact, it is now known that the ascending arousal system contains two major branches, each comprising discrete cell populations and neurotransmitters (7).



(Fig. 1). A schematic drawing showing key components of the ascending arousal system. Adapted from Saper 2005, pg 1258 (7).

Anesthetics could cause a loss of consciousness by pressing a switch in any (or all) of these regions (8). A study presented by Luo and Leung investigates whether the histaminergic system contributes to the neural mechanism of isoflurane anesthesia. The tuberomammillary nucleus is the sole source of histamine in the brain, and has been previously implicated in the actions of gamma-aminobutric acid–mediated anesthetics such as propofol and pentobarbital

(9,10) and the alpha-2 adrenoceptor agonist dexmedetomidine (11). Centrally active histamine receptor antagonists are known to cause sedation, and histamine levels are reduced during both natural sleep and anesthesia. However, the tuberomammillary nucleus sends projections to the entire brain, so exactly how histamine release produces behavioral and electroencephalographic arousal needs further investigation (8).

Dopamine (abbreviated as DA) is a monoamine neurotransmitter in the cathecolamine family and has a number of important physiological roles in the bodies of animals. In addition to being a catecholamine and a monoamine, dopamine may be classified as a substituted phenethylamine. In the brain, dopamine functions as a neurotransmitter being released by nerve cells to send signals to other nerve cells. Dopamine is produced in several areas of the brain, including the substantia nigra and the ventral tegmental area (12).

Several neurologic diseases are associated with dysfunctions of the dopamine system. Parkinson's disease, a degenerative condition that causes tremor and motor impairment, is caused by loss of dopamine-secreting neurons in the substantia nigra. Schizophrenia has been shown to involve elevated levels of dopamine activity in the mesolimbic pathway and decreased levels of dopamine in the prefrontal cortex (13,14). Attention deficit hyperactivity disorder (ADHD) (15) and restless legs syndrome (RLS) (16,17) are also believed to be associated with decreased dopamine activity.

Methylphenidate, better known as Ritalin, Concerta or Quillivant, is a stimulant drug widely used to treat attention deficit hyperactivity disorder. Methylphenidate is known to affect arousal-associated pathways controlled by the neurotransmitters dopamine, norepinephrine, and histamine (18). There is also evidence that methylphenidate increases cortical concentration of acetylcholine secondarily to enhanced dopaminergic transmission. A study done by Kuczenski and Segal (1997) showed that an acute dose of amphetamine increased the extracellular noradrenalin, dopamine and serotonin concentration in rat brain. In the same study, methylphenidate only enhanced the concentrations of noradrenaline and dopamine. It was concluded that acute methylphenidate administration increases extracellular dopamine and noradrenalin, consistent with its presumed mechanism of action as an uptake inhibitor of these nerve terminal transporters. The absence of an effect of methylphenidate on caudate-putamen

extracellular serotonin at doses that produce intense, focused sterotypies was considered to suggest that a stimulant induced increase in serotonin is not a prerequisite for the appearance of perseverative behaviors. There is clinical evidence suggesting that methylphenidate is a behavior-altering drug utilized to counteract barbiturate depression, barbiturate and non-barbiturate lethargy in psychiatric patients (18).

Methylphenidate enhances cognitive performance in adults and children diagnosed with ADHD, and also in healthy volunteers, on tasks that are sensitive to frontal lobe damage including aspects of spatial working memory. Mehta et al. (2000a) investigated changes in regional blood flow induced by methylphenidate during the performance of a spatial working memory task in normal subjects. The result of this study showed that improvements in working memory performance occur with task-related reductions in cerebral blood flow in the dorsolateral prefrontal cortex and posterior parietal cortex. Thus methylphenidate appears to improve spatial working memory which may be of relevance to its beneficial effects.

There is also evidence to suggest that methylphenidate improves depression in many patient groups including: stroke patients (Lazarus et al., 1992; Masand and Chaudhary, 1994), cancer patients (Fernandez and Adams, 1986; Fernandez et al., 1987; Olin and Masand, 1996), those with HIV infection (Holmes et al., 1989; Fernandez et al., 1995) and secondary to surgery or medical illness (Kaufmann et al., 1984; Woods et al., 1986; Masand et al., 1991). Finally, it may be effective in the treatment of neurocardiogenic syncope (Grubb et al., 1996) and for reducing the duration of coma (Worzniak et al., 1997).

Methylphenidate is useful in the treatment of depression in cancer patients (Fernandez et al., 1987; Stiebel and Kemp, 1990; Olin and Masand, 1996; Macleod, 1998). Furthermore, Fernandez and Adams (1986) report improvements in both depression and cognitive impairment following methylphenidate administration. Similarly, in HIV-infected patients the therapeutic efficacy of methylphenidate in the relief of depression secondary to HIV-infection is well established (Fernandez et al., 1988; Holmes et al., 1989; White et al., 1992; Fernandez et al., 1995). Methylphenidate has also been shown to produce a significant improvement on measures of attention and learning that was impaired in children who had survived acute lymphoblastic leukemia or malignant brain tumors (Thompson et al., 2001).

A group of researchers from MIT and Harvard Medical School conducted an experiment to see whether methylphenidate could stimulate arousal in rats receiving the anesthetic drug isoflurane. The first experiments showed that animals receiving intravenous methylphenidate five minutes before the discontinuation of isoflurane recovered significantly faster than did rats receiving a saline injection. Another experiment showed that methylphenidate induced signs of arousal (e.g. movement, standing up, etc.) in animals continuing to receive isoflurane at a dose that would have been sufficient to maintain unconsciousness. EEG readings taken during that experiment showed that brain rhythms associated with arousal returned within 30 seconds of methylphenidate administration. Giving a drug that interferes with the dopamine pathway blocked the arousal effects of methylphenidate, supporting the role of that pathway in the drug's effects (19). These results call for further studies to be done to assess the response of humans to methylphenidate administration while under anesthesia.

Use of methylphenidate as a central nervous stimulant to test its arousal effect in humans may be a clinical concern regarding potential interaction with general anesthesia outcome.

Peripheral actions might include an increase of systolic and diastolic blood pressure and a weak bronchodilator and respiratory stimulant action.

The central nervous system action of amphetamines appears to be associated with local release of biogenic amines such as norepinephrine from nerve terminal storage sites (20).

It is reported that chronic amphetamine exposure and stimulation of the adrenergic and peripheral nerve terminals causes a depletion of catecholamine receptor storage (21).

Oral methylphenidate, at therapeutic dosage 40 – 60 mg/day, is known to exert undesirable cardiovascular effects, including increases in both blood pressure (BP) and heart rate (HR), and there is evidence that these effects are related to increased concentrations of circulating catecholamines. During an interval from 1 to 8 hours after dosing, a single dose of methylphenidate increased HR with a maximal effect of about 25 bpm at 2.5 hours (31).
Single doses of methylphenidate alone increased BP from 1 to 8 hours (by an average of 10 mmHg), and from 0.5 to 3 hours (by 12 mmHg) after dosing, respectively (31).

ADHD patients with a history of long-term use of CNS stimulants may have a blunted ability to respond to intraoperative hypotension as a result of depletion of catecholamine stores, or receptor downregulation (33).

Dodson and Fryer studied the analeptic and analgesic proprieties of methylphenidate in naïve methylphenidate users undergoing abdominal surgeries under general anesthesia There was a highly significant increase ($P< 0.001$) in heart rate 5 minutes and 10 minutes after methylphenidate administration compared to placebo. They noticed a mean increase in systolic blood pressure at 5 minutes in halothane-methylphenidate group of 2.14 kPa. One dysrhythmia was seen in a patient receiving halothane and methylphenidate. Normal rhythm was restored by administering neostygmine and atropine.

One patient experienced catatonic effect lasting 40 minutes, with no possible communication, the patient responding non-purposefully to painful stimuli.

Methylphenidate being used more often for several medical conditions (ADHD, narcolepsy, hypersomnia), legitimate concerns are raised regarding the preoperative use and its potential interaction with halogenated anesthetics and cardiac stability of surgical patients undergoing general anesthesia (22).

Drug-naive psychiatric adult inpatients given methylphenidate orally in high test doses (e.g., 1 mg/kg) showed increases in heart rate averaging 12 beats/min and increases in systolic blood pressure averaging 5 mmHg (39). In a study of low test doses (15 mg) of methylphenidate given to normal adult volunteers, no significant cardiovascular changes resulted (40). In the study done by Martin et al. (1971), subcutaneous administration of methylphenidate 60 mg rapidly caused tachycardia and hypertension. Intravenous administration of high doses of methylphenidate yielded even more striking and rapid cardiovascular changes: e.g., heart rate increases of 39 beats/min, diastolic blood pressure increases of 16 mmHg and systolic blood pressure increases of 32 mmHg. There is no doubt that parenteral methylphenidate substantially elevates heart rate and blood pressure in a dose-dependent fashion in drug-naive adults (39).

In the work of Wilens et al (34) methylphenidate was associated with a minor but statistically significant increase in heart rate. Methylphenidate has also occasionally been reported to

induce cardiac arrhythmias (35). Based on these findings, careful titration of the anesthetic agent is important to avoid unexpected hemodynamic changes during general anesthesia.

Children taking stimulant medication for ADHD, and who ingest medication on the day of surgery – before surgery - do not appear to have altered BIS or depth of anesthesia at 1 MAC of halogenated anesthetics at induction or during the course of surgeries (23).

General anesthesia with epidural anesthesia was administered to two patients taking methylphenidate, both cases for total hip replacement. One patient was able to stop taking methylphenidate five days before the surgery and the other patient did not stop the treatment. Both cases needed more anesthetics than usual on induction, but stable condition could be maintained during and after the surgery. The article concluded that it is possible to perform general anesthesia safely for patients taking a usual dose of methylphenidate (32).

The reports of ADHD children in which the amphetamine drug was not stopped preoperatively concluded that halogenated anesthetics may be successfully used with preoperative administration of methylphenidate without any need to modify the standard anesthesia protocol. No dramatic fluctuation in arterial blood pressure was observed (22).

The patients had been taking Concerta, a once-daily, long acting formulation of methylphenidate – same type of formula that we intend to use in our study. Complete blood count, electrolyte profile, chest X-ray, and electrocardiogram obtained before the operation were within normal limits. Anesthesia was induced with propofol, atropine, fentanyl, and cisatracurium, and was maintained with sevoflurane in oxygen, and cisatracurium. No episode of seizure, arrhythmia or cardiovascular instability was noted throughout the entire anesthetic course. The patients had been discharged from hospital without any complications (24).

Several potential interactions between anesthetics and ADHD drugs have been postulated; however, there are little data to confirm the clinical significance of these interactions (37).

One potential consequence of anesthetic-ADHD drug interaction may be inadequate sedation, methylphenidate antagonizing the effect of midazolam in conscious sedation (38).

Acute intravenous administration of dextroamphetamine (DA) 0.1/ 0.5, and 1 mg/kg, during halothane anesthesia in dogs was associated with increases of MAC to 19 +/-8, 67 +/- 11, and

96 +/- 15% above control values. These data support the hypothesis that catecholamines that act on the central nervous system may alter anesthetic requirements(42).

Emergence delirium is explained as a psychomotor agitation accompanying emergence from general anesthesia, with no lucid interval - the patient manifesting alterations in mental status as disorientation, confusion, hallucinations, hypersensitivity to stimuli, restlessness, and hyperactive physical behavior that may be violent and harmful - Diagnostic and Statistical Manual of Mental Disorders - DSM-IV (30).

ED is a significantly intricate syndrome, with a multitude of contributing factors and manifestations. In order to fully appreciate the nature of ED, it must be considered from a biological (eg, medication, blood pressure, metabolism), psychological (eg, pre-morbid psychiatric condition, separation anxiety), and social (eg, parental anxiety, parental presence, pre-surgical preparation) standpoint (29).

An acute upregulation of inhibitory tone within the brain acts to further disrupt network connectivity in vulnerable patients predisposed by reduced baseline connectivity precipitating a delirium (41).

Reports of emergence delirium, also referred to in the literature as emergence agitation (EA) or post-anesthetic excitement, diagnosed in patients with a history of methylphenidate use, were associated with premorbid predictors in children (attention deficit hyperactivity disorder - ADHD). It was noted that the administration of an opioid reduced ED (22, 24, 29).

Dopamine is known to interact with acetylcholine and is upregulated in delirium states. The therapeutic effect of Haloperidol, a dopamine blocker, on delirium suggests that dopamine may have an indirect effect on delirium via its anticholinergic activity (41).

Dodson and Fryer described two situations when methylphenidate was administrated as an IV form (20mg) to stop postoperative shivering. Both patients became unconscious. The patients recovered after manual ventilation with oxygen, furosemide and prednisolone IV (36).

A review done by Stiefel and Besag (25) in 2010 regarding the cardiovascular safety of neurostimulants, analyzed the effects on blood pressure (BP), heart rate (HR), ECG parameters and the risk of sudden death and concluded that methylphenidate appears to cause subclinical

increases in BP and HR. There is growing evidence to suggest that amphetamines do not cause statistically or clinically significant increases in QTc.

Kratochvil et al. studied children assigned to either atomoxetine or methylphenidate. There

were statistically significant increases in mean HR, systolic blood pressure (SBP) and diastolic blood pressure (DBP) of 5.65 bpm, 3.35 mmHg and 2.95 mmHg, respectively. The study concluded that methylphenidate use resulted in a statistically significant increase in HR and BP and that the effects were not thought to be clinically significant.

Safer (26) reviewed the cardiovascular safety of psychostimulants in ADHD. Four studies evaluated ECG data read by cardiologists. No cardiac irregularities were noted except for an increased HR in one study.

Most studies investigating the safety of methylphenidate in those with chronic traumatic brain injury (TBI) have found little evidence of significant side-effects. Methylphenidate administration resulted in a statistically significant increase in pulse of 12.3 beats/min, diastolic blood pressure of 4.1 mmHg, and mean arterial pressure of 3.75 mmHg. These changes did not, however, appear to be symptomatic, as no participants were withdrawn due to adverse events, and there was no significant self-report of increase heart rate with methylphenidate. Conclusion: Methylphenidate given at 0.3 mg/kg body weight appears to be safe in the inpatient rehabilitation phase (27).

Winnie and Collins compared analeptic drugs activity when given post operatory in healthy female patients undergoing breast biopsy with thiopental as an induction agent. 5 out of 8 patients, in the methlphenidate group, presented neuromuscular signs of CNS stimulation ranging from hyper-reflexia to intermittent clonic activity (43).

Two healthy females, naïve methylphenidate users, received 20 and 60 mg of methylphenidate IV form at the end of dilatation and curettage procedure performed under surital and nitrous oxide anesthesia. Both of them experienced episodes of restlessness, euphoria and headache. Methylphenidate was effective in antagonizing the severe depression of barbiturate induced anesthesia, otherwise, the high incidence of restlessness, euphoria and mental agitation following its IV administration in moderate doses make it unfavorable for routine use (18).

Brichard and Johnstone studying post-halotane muscular spasticity noticed that methylphenidate could have a dangerous sympathomimetic effect in the presence of hypercapnia, thyrotoxicosis or in hypertensive patients. The suppressor effect - increased vagal tonicity - was achieved using neostigmine and small doses of beta-blocking agents (44).

The review of literature regarding chronic and naïve methylphenidate users undergoing elective surgeries under general anesthesia, implies that safety issues are of great importance when designing phase I studies involving central nervous stimulant drugs. Continued multi-modal monitoring and vigilance with regard to any suspected adverse effects, including cardiovascular effects will help to fill the informational gap with regards to unknown cardiovascular side effects, emergence delirium incidence and perioperatory awareness.

Due to the potential risk of drug related serious side effects, any clinical evidence of a serious adverse event will place the study on clinical hold until a full assessment and decision is made by the responsible parties.

II. HYPOTHESIS:

Based on this significant arousal stimulatory effect, we hypothesize that methylphenidate (inhibitor of dopamine and norepinephrine transporters) decreases the emergence time from isoflurane general anesthesia.

III. PRIMARY OBJECTIVE:

To assess whether methylphenidate affects time of emergence from isoflurane general anesthesia. Time to emergence was defined as the time from termination of isoflurane to extubation. After stopping isoflurane infusion, when the patient breaths spontaneously with adequate tidal volume and respiratory rates, the trachea will be extubated and the time will be recorded.

IV. SECONDARY OBJECTIVES:

- To assess the efficacy of methylphenidate in preventing post operative nausea and vomiting (PONV) by limited opioids consumption: PONV verbal response scale on a 0 to 10 verbally elicited scale: 0 (no nausea) to 10 (nausea as bad as it could be). .

- To assess the efficacy of methylphenidate in preventing opioids dose escalation (fast cognitive improvement with efficient pain control -Postoperative Pain Numeric Rating Scale: O=None; (1-3)=Mild; (4-6)= Moderate; (7-10)=Severe).

V. EXPERIMENTAL METHODS:

i. Study Population:

- Adult patients at Ohio State University Wexner Medical Center – Sports Medicine, aged between 18-65 years, with an American Society of Anesthesiologists (ASA) physical status of I (normal healthy patient) or II (patients with mild systemic disease; no functional limitation) who are scheduled to undergo hip arthroscopic surgery – same day discharge - under isoflurane general anesthesia.

ii. Sample Size:

54 subjects who give written informed consent to participate in the study and who meet all inclusion and no exclusion criteria will be included in the study.

iii. Sample Size Calculation / Statistical Methods

For continuous data, we will use linear mixed models and t-tests for group differences. For discrete data, we will use nonparametric Wilcoxon test for testing.

With a 1:1 randomization ratio of two arms, n=27 patients per group will provide 80% power to detect a difference of 7 minutes in time of emergence assuming a standard deviation of 9 with an alpha level of 0.05 for a two sample t-test.

iv. Inclusion Criteria:

- Male or female , 18 to 65 years of age
- ASA I or II
- Capable and willing to consent
- Participants literate in English language

v. Exclusion Criteria:

- ADHD with current use of methylphenidate
- Hypersensitivity to methylphenidate
- ASA III, IV or V
- Patients with severe visual or auditory disorder
- Illiteracy
- Presence of a clinically diagnosed anxiety, agitation, major psychiatric condition such as bipolar disorder, uncontrolled major depression, schizophrenia
- Tics or Tourette's syndrome
- Glaucoma
- Uncontrolled hypertension, defined as history of hypertension with a baseline blood pressure greater than 140/90 mmHg
- History of atrial arrhythmias (atrial fibrillation, atrial flutter) and myocardial infarction
- Taking or have taken within the past 14 days a monoamine oxidase inhibitor or MAOI (Selegiline)
- Subjects who have participated or are currently participating in a clinical trial of an investigational drug within 30 days prior to surgery
- Any condition, which in the opinion of the investigator would make subject ineligible for participation in the study such as history of unstable cardiovascular, pulmonary, renal, hepatic, neurologic (seizures), hematologic or endocrine abnormality (hyperthyroidism, unstable Diabetes type I/II)

VI. STUDY DESIGN

Single-center, prospective, randomized, double-blind, placebo-controlled trial involving 54 subjects scheduled to undergo arthroscopic orthopedic surgery under isoflurane general anesthesia at The Ohio State University Wexner Medical Center (OSUWMC) – University Hospital East. Eligible subjects that provide voluntary and written informed consent will be included in this study.

VII. DATA SAFETY MONITORING

Regular data verification and protocol compliance checks (every 3 months) will be performed by a data manager (biostatistician), two attending anesthesiologists and the principal investigator. IRB will be provided with feedback on a regular basis, including findings from adverse-event reports and conclusions derived from data safety monitoring.

Monitoring will also consider factors external to the study when interpreting the data, such as scientific or therapeutic development, the safety of study participants and that they do not incur undue risks. The risks versus benefits will continually be reassessed throughout the study period. Participants will be fully informed of the study requirements throughout the conduct of the trial and will be allowed the opportunity to withdraw from participation at any moment during the study.

The investigators will protect the health and safety of participants, inform participants of information relevant to their continued participation, and will pursue the research objectives with scientific diligence.

Based on investigational new drug (IND) FDA policy, the PI of the study has agreed that Institutional Review Board (IRB) will be responsible for initial and continuing review and approval of each of the studies in the proposed clinical investigation and accurate records will be available for inspection in accordance with CFR 312.68.

The safety reports will determine that an adverse event occurring during a clinical trial is both "serious" and "unexpected" and also is a "suspected adverse reaction."

These reports will be made to FDA, IRB and to all investigators part of the clinical trial.

Based on FDA determination:

- If the precise event type – of equal severity and specificity – has not been declared as having been observed in people taking the particular drug under study, then the event is "unexpected" under the rule.

- A "suspected adverse reaction" will be considered any adverse event for which "there is evidence to suggest a causal relationship" between the drug and the event.

Unblinding – During this process the allocation code will be broken so that the investigator, attending physicians and clinical staff and/or the trial statistician will become aware of the intervention for a person participating in a trial.

Unblinding envelopes , each labelled with the randomisation number that contain the allocation for that person, will be opened if emergency unblinding is required.
Unblinding will be required:
− To make clinical treatment decisions or when an unexpected serious adverse event occurs and the intervention must be made known (emergency unblinding).
- At the request of the data safety monitoring group
− At the conclusion of the study to determine the effect of the intervention.

The PI, in consultation with the clinical team will assess the need for unblinding to enable clinical treatments to be planned.
The allocation code will be determined according to the randomization table held within the envelope.
An unblind request form will be filed for later audit.
Data safety monitoring group will analyse the unblind report and will determine if an immediate unmasked analysis is required.

i. Preoperative Assessments

After signing the inform consent within 30 days of arthroscopy, subjects will undergo screening procedures in the morning of surgery, prior to administration of study treatment.

There are no activities for the participant in the days between consent and surgery.

The research staff will collect the subject's medical history, demographics (including gender, age, years of education, race, and ethnicity), history of alcohol or drug abuse, history of smoking, and allergies. All medication taken in the previous 7 days prior to treatment day will be recorded. Vital signs, ECG recording, urine pregnancy test and a physical examination will be performed at this time. Adverse events and serious adverse events will be recorded from time of consent until last patient follow-up. Apfel score will identify patients at risk for PONV.

ii. Montreal Cognitive Assessment (MoCA) will be done at baseline, and 90 minutes post extubation ± 40 minutes.

MoCA was designed as a rapid screening instrument for mild cognitive dysfunction. It assesses different cognitive domains: attention and concentration, executive functions, memory, language, visual constructional skills, conceptual thinking, calculations, and orientation. Time to administer the MoCA is approximately 10 minutes. The total possible score is 30 points; a score of 26 or above is considered normal.

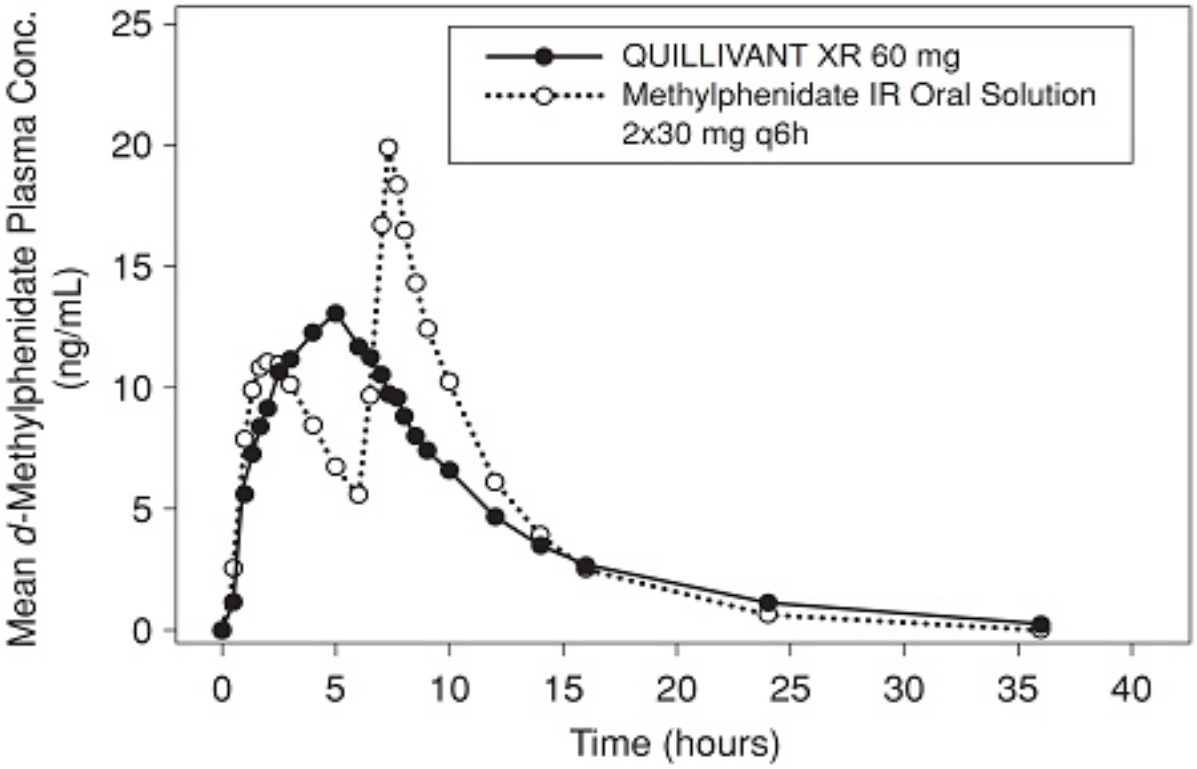
iii. Randomization and Blinding

Randomization should take place after completion of preoperative testing session. Patients who are discontinued from study participation prior to randomization will be dropped from the study and no further information will be collected.

Upon enrollment, subjects will be randomly assigned in a 1:1 ratio by the research pharmacist from a pre-determined randomization schedule to one of two study groups:

Group 1: Quillivant XR - Methylphenidate HCL Extended Release oral suspension – (after reconstruction with water – 5mg/mL) 20 mg (PO)

Group 2: 20 mg Placebo (PO)



Mean d-Methylphenidate Plasma Concentration-Time Profiles

The relative bioavailability of Quillivant XR compared to Methylphenidate IR oral solution (2×30 mg, q6h) is 95%

The placebo form will be provided by Ohio State University Wexner Medical Center Pharmacy.

All subjects will receive liquid formula - 4 mL suspension of study drug, within 2 hours prior to the incision time

Based on the new data, most national anesthesiology societies now recommend no more than 2 hours fasting for clear fluids (water, tea, coffee, pulp-free fruit juices) in elective patients, both adults and children and including pregnant women not in labor (Anesthesiology 2011; 114: 495-511). Oral benzodiazepines are commonly used for premedication 2 hours prior surgery per standard operating procedures.

iv. Parameters for General Anesthesia

All the subjects will receive a standardized general anesthesia. Standard monitoring will include ECG, non-invasive arterial pressure, SpO_2, and measurements of end-tidal carbon dioxide, isoflurane concentration, BIS and Cerebral Oximetry.

BP, HR and RR will be recorded every minute during induction, every 3 minutes during maintenance and every minute during emergence by a trained Clinical Research Coordinator (CRC) on the Case Report Form (CRF). In addition, de-identified electronic records for BP, HR and RR may be obtained.

Baseline systolic arterial pressure will be defined as the lower of the two measurements obtained during screening and pre-induction phase.

All subjects will be premedicated with intravenous midazolam (1-2 mg) and a ≥ 500 ml bolus of lactated Ringer's solution. Standard monitors will be applied and a forearm vein will be cannulated for infusion of intravenous fluids.

Induction Phase

Preoxygenation will be achieved with 100% oxygenation for at least 5 full Tidal Volume .

Anesthesia will be induced with intravenous fentanyl (1-2 ug/kg) and intravenous propofol (1-2.5 mg/kg). After loss of consciousness, the airway of the patient will be secured with an endotracheal tube or laryngeal mask, airway (LMA). When the patient is intubated a neuromuscular-blocking agent – rocuronium (0.4-0.6 mg/kg) will be administered to facilitate airway manipulation, immediately after propofol administration.

During the induction phase, the following information will be recorded:

- Induction Phase Start Time – Time of First Propofol Bolus
- Time of Loss of Count
- Time of Loss of Eyelash Reflex

- Airway Manipulation Start Time – Start Time of Laryngoscopy
- Airway Manipulation End Time
- Any Reaction to Airway Manipulation

In addition, the HR, BP and RR will be calculated with an increased frequency, with at least one recording every minute or when any significant event occurs, beginning from induction start time for a period of 15 minutes.

Maintenance Phase

Anesthesia will be maintained using isoflurane and boluses of fentanyl as needed. Additional neuromuscular blocking agents (rocuronium - every 50 minutes) will be administered at the discretion of the anesthesiologist.

All patients will be assessed for signs of inadequate anesthesia (hypertension, tachycardia or somatic response), hypotension, or bradycardia. Any of these unwanted intra-operative responses, which required intervention, will be recorded.

Any significant change in blood pressure exceeding 20% from the acceptable baseline value - Systolic Blood Pressure ≤120mmHg and Diastolic Blood Pressure ≤80mmHg - will be managed increasing Isoflurane concentration and/or administering hydralazine or labetolol depending on the heart rate as a second line based on the judgment of the anesthesiologist.

Anesthesia will be standardized and maintained with isoflurane within the range of MAC 0.92 1.38 (age adjusted) according to our accepted standard operating procedure. MAC has been defined as the "minimum alveolar concentration of anesthetic at 1 atmosphere that produces immobility in 50% of those patients exposed to a noxious stimulus" (28). The fresh gas flow should be kept at 2 liters/min.

End-tidal isoflurane, and total amount of propofol and fentanyl consumed will also be recorded.

During the maintenance phase, the following information will be recorded:

- Maintenance Phase Start Time – Start Time of Isoflurane Administration
- First Incision Time
- All Unwanted Intraoperative Somatic and Autonomic/Hemodynamic Responses

The emergence process will be started at a time found appropriate by the anesthesia provider. After the last suture is done the isoflurane will be turned off and the fresh gas flow will be increased to 10 l/min. This point in time will be recorded. The patient will be extubated when he meets the common extubation criteria (open eyes, respond to command, regular respiration, and adequate hand grip strength). This point in time will be recorded as well.

The BIS recording will continue during the emergence process.

Anesthesia procedure start time and extubation time will be recorded.
At the end of the surgery if the respiratory rate (RR) is more than 30rpm fentanyl will be titrated at 50mcg until respiratory rate of less than 20 rpm.
Pain control management will be accomplished with Tylenol (1000 mg IV) and Ketorolac (30mg IV).
After extubation the patient will receive O2 via nasal cannula and if stable - vital signs and appropriate respiration are present - the patient will be transferred to the Recovery Room.
During the emergence phase, the following information will be recorded:

- Emergence Phase Start Time – Time when Anesthesia is Adjusted to Facilitate Rapid Recovery
- Recovery Start Time / Anesthesia Stop Time – Time when Isoflurane Administration is Discontinued
- Last Surgical Suture Time

Recovery Phase

After the termination of anesthesia, patient recovery will be observed continuously by the primary anesthesiologist in the Operating Room (OR) and the following information will be recorded:

- Time of First Reaction
- Time of Eye Opening

- Time of Response to Simple Verbal Command – Prompted every 30 seconds
- Time of Extubation / Removal of LMA
- Time of Readiness to Transfer to Post-Anesthesia Care Unit (PACU)

v. Processed EEG

Bispectral monitoring (BIS) will be utilized in all subjects (Monitor description provided by the Covidien Company).

The BIS Vista Monitoring System (Aspect Systems, Norwood, MA) will be used to measure processed EEG. In preparation for each case, the BIS Vista will be plugged in and the time and date will be set to correspond with the time standard for the anesthesia record.

Prior to the beginning of anesthesia one BIS sensor will be applied to the forehead. The monitor will be checked to assure that the sensor check is passed for all four points and that monitoring ensues. Anesthetic titration will be as per standard procedure. BIS data will be collected for the entire case. Instructions will be provided to download the data onto a USB data stick.

vi. Cerebral Oximetry

For the study purposes we will use Covidien Company monitor (description).
Prior to the beginning of anesthesia and prior to the beginning of the study drug infusion, FORE-SIGHT probes should be applied to the forehead. The monitor should be checked to assure that the sensor check is passed and that monitoring ensues.
Cerebral oximetry, based on near infrared spectroscopy (NIRS) technology, provides information on the availability of oxygen in brain tissue at risk during numerous pathological conditions. Cerebral oximetry measures local concentrations of hemoglobin (oxy- and deoxy-), and regional cerebral tissue oxygen saturation ($SctO_2$) at the microvascular level (arterioles, venules, and capillaries only). As a result, cerebral oximetry $SctO_2$ is a mixed oxygen saturation parameter which has a value between arterial (SaO_2) and jugular venous oxygen saturation ($SjvO_2$) under normal physiological conditions, therefore $SaO_2 > SctO_2 > SjvO_2$. Complementary to the arterial

oxygen saturation (SaO_2) measured by pulse oximetry, $SctO_2$ reflects regional cerebral metabolism and the balance of local cerebral oxygen supply/demand.

vii. Post Anesthesia Care Unit (PACU)

In the PACU patients will be assessed using instruments specific for the PACU - Fitness for Discharge, Quality of Recovery Score, Postoperative Pain Numeric Rating Scale: O=None; (1-3)=Mild; (4-6)= Moderate; (7-10)=Severe.

The investigator or nursing staff will evaluate vomiting numerically as: 0 (no vomiting), 1 (mild vomiting), 2 (moderate vomiting) or 3 (severe vomiting).

Nausea severity will be assessed with the use of a verbal response scale on a 0 to 10 verbally elicited scale: 0 (no nausea) to 10 (nausea as bad as it could be).

MoCA scale for cognitive status will be performed at 90 minutes after extubation ± 40 minutes.

Admission and discharge time to the post-anesthesia care unit (PACU) will be recorded.

Most of the patients are able to leave the hospital in the same day of surgery with a prescription of oxycodone/acetaminophen for pain, and aspirin to lower the risk of deep vein thrombosis (DVT). Hip Arthroscopy has the benefit of being minimally invasive procedure, producing less muscle damage than open techniques with faster recovery and ability to return quicker to normal function.

The patient has the option to stay at the hospital overnight after surgery.

viii. Safety Assessments:

Safety parameters will be assessed by monitoring vital signs, ECG and adverse events. The occurrence of adverse events (AE) and serious adverse events (SAE) will be recorded during the 72 hours post-operative period (follow up phone calls are done by the surgeon's physician assistant). For each adverse event the relationship to the study medication, severity, expectedness of an adverse event and outcome will be determined by the Principal Investigator and recorded in the study source accordingly.

All study medication and study procedures required by protocol that are not considered as part of the standard of care, and that will be obtained solely for research purposes, will be provided

by the study at no cost to the subjects**.** In the case a subject withdraws from the study because of a serious adverse event (SAE) the local IRB will be notified within 24 hours.

ix. Pharmacokinetics (PK) Blood Collection and Processing

Blood samples for determining the plasma concentrations of Methylphenidate at 90 minutes post extubation will be collected by direct venipuncture. Each blood sample (6 mL of whole blood per sample) will be collected into a pre-labeled tube containing dipotassium ethylenediamine tetraacetic acid (K_2EDTA) as the anticoagulant. Immediately after collection, each blood sample will be gently inverted a few times for complete mixing with the anticoagulant and placed on crushed ice or equivalent. Within 30 minutes of collection, each blood sample will be centrifuged for 15 min at approximately 1000 x g. Plasma will be harvested, transferred to a pre-labeled Penetrex-capped polypropylene tube and stored at or below -20°C.

x. Adverse event definition

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject receiving a medicinal product and which does not necessarily have a causal relationship with the study treatment. An AE can be any unfavorable and unintended sign, symptom, abnormal laboratory finding or a temporally disease associated with the use of a study drug, whether or not considered related to the study drug. For this study, an AE is defined as a 20% change from baseline value (e.g. SBP, HR) or as defined by an anesthesiologist. Planned hospital admissions and/or surgical operations for an illness or disease that existed before the subject was enrolled in a clinical study are not to be considered as AEs.

xi. Serious adverse event

A SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
- Results in persistent or significant disability/incapacity
- Requires in-subject hospitalization or prolongs hospitalization
- Is a congenital anomaly/birth defect
- Is another medically significant event that, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

xii. Withdrawal Criteria from the study.

According with the Declaration of Helsinki, participants have the right to withdraw from the study at any time for any reason. The principal investigator also has the right to remove a subject from the study. Reasons for which a subject may be removed from the study include:

- An adverse event
- The request of the subject, his/her legal representative or caregiver, investigator, whether for administrative or other reasons
- Non - compliance with medication, protocol violation or unreliable, behavior
- Any clinically significant abnormal laboratory values, or other clinically significant abnormalities identified by the principal investigator according to his clinical judgment, will be followed by appropriate tests and/or procedures until these values have returned to normal or to clinically acceptable levels or can be attributed to other causes other than study drug.

The principal Investigator may withdraw an enrolled and treated subject from the study for any of the following reasons:

- Occurrence of a serious or intolerable adverse event.
- Emergence of a clinically significant change in a laboratory parameter(s).
- The subject requests to be discontinued from the study.
- A protocol violation sufficiently serious as to require subject withdrawal. General or specific changes in the subject's condition that render further treatment unreasonable or unsafe within the standards of clinical practice in the judgment of the Principal Investigator or treating physician. Any subject may leave the study at any time. If the subject decides to stop participating in the study, there will be no penalty. The subjects will not lose any benefits to which they are otherwise entitled.

xiii. Follow Up Phone Call 24 Hours / 48 Hours/ 72 Hours

Activities of Daily Living Assessment (ADL)

The original ADCS-ADL Inventory is a comprehensive battery of ADL/Instrumental ADL questions aimed to measure functional ability of patients over a broad range of cognitive impairment. Each ADL item comprises a series of hierarchical sub-questions, ranging from the highest level of independent performance of each ADL to complete loss. The inventory is administered as an interview to the patient's study partner and covers the patient's most usual and consistent performance of each ADL during the previous 4 weeks. The ADL Inventory was adapted by the ADCS from the original ADCS-ADL Inventory and retains the same structure of hierarchical subquestions. There are 24 items in the ADCS-MCI-ADL. The score range for items 1 - 18 is 0 – 53.

References:

1. Franks NP: General anaesthesia: From molecular targets to neuronal pathways of sleep and arousal. *Nat Rev Neurosci* 2008; 9:370–86
2. Marcus, Mary Brophy. "How Does Anesthesia Work? A State That Is Nothing Like Sleep: No Memory, No Fight-or-Flight Response, No Pain." *U.S. News & World Report* 123 (August 18, 1997): 66.
3. Saper, C.B., Scammell, T.E., Lu, J. (2005) Hypothalamic regulation of sleep and circadian rhythms. *Nature*, 437,1257-1263.
4. Von Economo, C. (1930) Sleep as a problem of localization. *J.Nerv. Ment. Dis*., 71, 249-259.
5. Moruzzi, G., Magoun, H.W. (1949) Brain stem reticular formation and activation of the EEG. *Electroencelphalogr. Clin. Neurol*., 1,455-473.
6. Starzl, T.E., Taylor, C.W., Magoun, H.W. (1951) Ascending conduction in reticular activating system with special reference to thediencephalon. *J. Neurophysiol*., **14**, 461-477.
7. Saper, C.B., Chou, T.C., Scammell, T.E. (2001) The sleep switch:/hypothalamic control of sleep and wakefulness. *Trends Neurosci*.,**24**, 726-731
8. Anna Y. Zecharia, Ph.D., Nicholas P. Franks, Ph.D., F.R.C.A., F.Med.Sci., Biophysics Section, The Blackett Laboratory, Imperial College of Science, Technology, and Medicine, London, United Kingdom
9. Nelson LE, Guo TZ, Lu J, Saper CB, Franks NP, Maze M: The sedative component of anesthesia is mediated by GABAA receptors in an endogenous sleep pathway. *Nat Neurosci* 2002; 5:979–84.
10. Zecharia AY, Nelson LE, Gent TC, Schumacher M, Jurd R, Rudolph U, Brickley SG, Maze M, Franks NP: The involvement of hypothalamic sleep pathways in general anesthesia: Testing the hypothesis using the GABAA receptor beta3N265M knock-in mouse. *Journal of Neuroscience* 2009; 29:2177–87
11. Nelson LE, Lu J, Guo T, Saper CB, Franks NP, Maze M: The alpha2-adrenoceptor agonist dexmedetomidine converges on an endogenous sleeppromoting pathway to exert its sedative effects. *Anesthesiology* 2003; 98:428–36
12. Ian P. Stolerman (2 August 2010). *Encyclopedia of Psychopharmacology*, Volume 2. Springer Publishing. ISBN 3540686983.

13. Davis, K.L., Kahn, R.S., Ko, G., Davidson, M. (1991) Dopamine in schizophrenia: a review and reconceptualization. *American Journal of Psychiatry* 148:1474–1486.
14. Goldman-Rakic, P.S,. Castner, S.A., Svensson, T.H., Siever, L.J., Williams, G.V., (2004):Targeting the dopamine D1 receptor in schizophrenia: insights for cognitive dysfunction. *Psychopharmacology*,174: 3–16
15. "Patients' Brains May Adapt to ADHD Medication". *Neuroscience News*. April 4, 2012. http://neurosciencenews.com/adhd-medication-patient-brains-adapt-dat/. Retrieved April 4, 2012.
16. Allen, R (2004). "Dopamine and iron in the pathophysiology of restless legs syndrome (RLS)". *Sleep Medicine* **5** (4): 385–91.
17. Clemens, S.; Rye, D; Hochman, S (2006). "Restless legs syndrome: Revisiting the dopamine hypothesis from the spinal cord perspective". *Neurology* **67** (1): 125–130. doi:10.1212/01.wnl.0000223316.53428.c
18. P. B. Percheson, M.D., F.R.C.P.(c), John J. Caroll, B.A., M.D., CM., Guy Screech, M.A., M.B.,: Ritalin® (Methylphenidate): Clinical Experiences. *Canadian Society of Anesthesiology Journal*., vol. 6, no. 3, July, 1959
19. Ken Solt, M.D., Joseph F. Cotten, M.D., Ph.D., Aylin Cimenser, Ph.D., Kin F. K. Wong, Ph.D., Jessica J. Chemali, B.E.,Emery N. Brown, M.D., Ph.D. : Methylphenidate Actively Induces Emergence from General Anesthesia. 2011, the American Society of Anesthesiologists, Inc. LippincottWilliams & Wilkins. *Anesthesiology* 2011; 115:791–803
20. Carr LA, Moore KE. Norepinephrine release from brain by d-amphetamine *in vivo*. Science 1969;164:322–3
21. Hardman JG, Limbird LE. Amphetamine. In: The pharmacological basis of therapeutics. New York: McGraw-Hill, 1996;219–21.
22. Stephen P. Fischer, MD, Clifford A. Schmiesing, MD Cosmin G. Guta, MD, John G. Brock-Utne, MD, PhD: General Anesthesia and Chronic Amphetamine Use: Should the Drug Be Stopped Preoperatively? 2006 International Anesthesia Research Society; 203-206
23. Neil A. Chambers, Elaine Pascoe, Serge Kaplanian & Ian Forsyth; Ingestion of stimulant medications does not alter bispectral index or clinical depth of anesthesia at 1 MAC sevoflurane in children. Pediatric Anesthesia 22 (2012) 341–344

24. Cheng-Hsi Chang, Cheng-Fan Yang, Ying-Che Huang, Gau-Jun Tang, Kwok-Han Chan, Chien-Kun Ting: General Anesthesia in a Juvenile With Attentiondeficit Hyperactivity Disorder Accompanied by Long-term Use of Methylphenidate (Concerta®)
25. Gary Stiefel and Frank M.C. Besagt: Cardiovascular Effects of Methylphenidate,Amphetamines and Atomoxetine inthe Treatment of Attention-Deficit Hyperactivity Disorder. Drug Saf 2010; 33 (10): 821-842
26. Safer DJ. Relative cardiovascular safety of psychostimulants used to treat attention-deficit hyperactivity disorder. J Child Adolesc Psychopharmacol 1992; 2 (4): 279-90
27. Catherine Willmott, PhD1,3, Jennie Ponsford, PhD1,3,4, John Olver, MD2,3 and Michael Ponsford, MBBS2,3 Safety of Methylphenidate following traumatic Brain Injury: Impact on Vital Signs and Side-Effects During Inpatient Rehabilitation; J Rehabil Med 2009; 41: 585–587
28. Eger EI. Anesthetic Uptake and Actions. Baltimore: Williams and Wilkins, 1974; 1-3 Dion P. The cost of anaesthetic vapours. Can J Anaesth. 1992;39(6):633.
29. Gary M. Scott, MD, FAAP, Jeffrey I. Gold, PhD, Emergence delirium: a re-emerging interest, Seminars in Anesthesia, Perioperative Medicine and Pain Volume 25, Issue 3, September 2006, Pages 100–104 Pediatric Anesthesia American Psychiatric Association
30. (DSM-IV-TR) Diagnostic and Statistical Manual of Mental Disorders (ed 4), American Psychiatric Press, Washington, DC (2000) text revision
31. Ronan P. Kelly, MRCP, Kwee Poo Yeo, PhD, Choo-Hua Teng, PhD, Brian P. Smith, PhD, Stephen Lowe, PhD, Danny Soon, MD,Holly A. Read, MD, and Stephen D. Wise, FRCP. Hemodynamic Effects of Acute Administration of Atomoxetine and Methylphenidate; J Clin Pharmacol 2005 45: 851
32. Kasuga T., Meno A., Honda M., Masui. 2008 Jun; 57(6):748-51. General anesthesia for two patients taking methylphenidate.
33. Johnston RR, Way WL, Miller RD. Alteration of anesthetic requirement by amphetamine. Anesthesiology 1972;36:357−63.
34. Wilens TE, Hammerness PG, Biederman J, Kwon A, Spencer TJ, Clark S, Scott M, et al. Blood pressure changes associated with medication treatment of adults with attention-deficit/ hyperactivity disorder. J Clin Psychiatry 2005;66:253−9.

35. Gracious BL. Atrioventricular nodal re-entrant tachycardia associated with stimulant treatment. J Child Adolesc Psychopharmacol 1999;9:125−8.
36. Dodson, M.E., and Fryer J.E. (1980) Postoperative effects of methylphenidate. British Journal of Anesthesia 52(12): 1265-1270
37. Forsyth I, Riccardo B, Chambers N. Attention-deficit hyperactivitydisorder and anesthesia. Pediatr Anesth 2006; 16: 371–373.
38. Ririe D, Ririe K, Sethna N et al. Unexpected interaction of methylphenidate (Ritalin) with anesthetic agents. Paediatric Anaesthesia, 1997; 7: 69–72.
39. Janowsky DS, Leichner P, CloptonP, JuddLL, Parker D, Huey L: Comparison of oral and intravenous methylphenidate.Psychopharmacology 59:75-78, 1978
40. Gualtieri T, Hicks RE, Levitt J Conley, R, Schroeder SR: Methylphenidate and exercise: Additive effects on motor performance, variable effects on the neuroendocrine response. Neuropsychobiology 15:84-88, 1986
41. Sanders, Robert D. Hypothesis for the pathophysiology of delirium: Role of baseline brain network connectivity and changes in inhibitory tone. Follow Medical Hypotheses , Volume 77 (1) Elsevier – Jul 1, 2011
42. Johnston, Richard R. M.D.; Way, Walter L. M.D.; Miller, Ronald D. M.D. Alteration of Anesthetic Requirement by Amphetamine. 1972, American Society of Anesthesiologists, Inc
43. Winnie AP, Collins VJ.,The search for a pharmacologic ventilator. Acta Anaesthesiologica Scandinavica [Suppl], 63-71, 1966.
44. Brichard G. and Johnstone M., The effect of Methylphenidate (Ritalin) on Post-Halothane Muscular Spasticity, British Journal of Anesthesia (1970), 42, 718