A Short Review on Additional Therapeutic Effects and Adverse Effects of Sedative and Hypnotic Drugs

By

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A thesis submitted to the Department of Pharmacy in partial fulfillment of the requirements for the degree of

Bachelor of Pharmacy (Hons.)

Department of Pharmacy
Brac University
January, 2020

Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

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Approval

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Ethics Statement

There was no use of animals involved in this project.

Abstract

This study was conducted to list down the adverse effects and additional therapeutic effects of sedative hypnotic drugs through reviewed articles. There are different kinds of drugs as sedative hypnotic. Benzodiazepine and z-drugs is mostly used drug among those reported by the articles. Moreover the benzodiazepine causes severe adverse effects on older adults. The article reported that about 2.6 % older adult patient were affected by hip and other bone fracture for using benzodiazepine and other sedative hypnotic drugs to treat insomnia. Moreover other articles also reported that the pregnant women also have more chance to adverse effect for using sedative hypnotic drug. On the other hand, there is report for new molecule as sedative hypnotic drug called Indiplone showed anti aggregation effect on platelet with less adverse effects. Another articles reported that sedative hypnotic drug may used as analgesic drug. In addition there are some plant extract contain alkaloids, flavanoids used as sedative drug also showed different therapeutic effects. These extractions showed anti diabetic, sleep latency property. The articles were reviewed on both qualitative and quantitative analysis as well as in-vitro and in-vivo results were analyzed.

Keyword: Sedative, Hypnotic, Adverse effects, Therapeutic effects, In-vivo, In-vitro

Dedication

I want to dedicate this work to my respected parents for their continuous support.

Acknowledgement

At first, I want to thank Almighty Allah to give me the strength and ability to overcome all the difficulties and fulfill this project. Without Allah's mercy, It could never be possible to accomplish the purpose of the work.

After that, I would cordially like to thank my supervisor, of **Dr. Md.Abu Bakar**, Associate Professor, Department of Pharmacy, Brac University for his continuous support and guidance. I am very grateful to him because without his support this work would not be completed. I am also grateful to him for his best instructions and versatile knowledge. I also would like to thank our Chairperson Professor **Dr. Eva Rahman Kabir**, Department of Pharmacy, Brac University for her support.

Finally, I would like to thank to my parents and my friend who helped me to finish my work.

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List of Acronyms

AR	The Absolute Risk
RR	Relative Risk
CI	Confidence
SAS	Statistical Software
GABA	Gama Amino Butaric Acid
DEX	Dexmedetomidine
CO_2	Carbon dioxide
RSS	Ramsey Sedation Score
VPS	Verbal Pain Score
NPS	Numeric Pain Score
SSRI	Selective Serotonin Reuptake Inhibitor
SNRI	Serotonin-nor epinephrine reuptake inhibitor

Chapter 1

Introduction

1.1 Explanation of Sedative Hypnotic drugs

Anxiety is a mental disorder. Among all the mental disorder anxiety is most common and day by day it is becoming severe. Anxiety basically refers to unpleasant state of tension, uncasing apprehension. According to World Health Organization (WHO) report in 2017 about 7.5% people are affected by anxiety. To treat this disease, the drugs are used called sedative and hypnotic drugs. Basically, sedative hypnotic drugs are the chemical substances which are used to reduce anxiety and tension. Moreover, these types of drugs are also used for neurological disorder such as insomnia, amnesia. In addition for muscular disorder like muscle spasms sedative hypnotic drug are also used. Basically, same types of drugs are used as sedative and hypnotic. The main difference between sedative and hypnotic is in the amount of dose. The lower dose is used as sedative drug. On the other hand, higher dose is used as hypnotic drugs. Often drugs are referred as tranquilizers.In addition, the substance which having quieting or calming effect used as sedative hypnotic drugs. This drugs having tended to depress the central nervous system. Also, this action can obtain from other drug like opiates, which having distinctive characteristics of sedative hypnotic ability by gaining there effects without mood or reducing sensitivity to pain affected.

1.2 History of the development of sedative hypnotic drugs

Over the centuries, only alcohol and opium were the drugs which were available for neurologic treatment. In 1800s a liquid solution of bromide salts was introduced as a first sedative and as a hypnotic substance. After that in 1869, a synthetic sedative-hypnotic “Chloral hydrate” was introduced, which was derived from ethyl alcohol. This synthetic sedative-hypnotic was basically used notoriously (Knock-out) drops. In 1980s as a clinical

medicine, paraldehyde was introduced, which was followed as barbital synthesis in 1903. The commonly used drug Phenobarbital was becoming available in the 1912. In the next twenty years barbiturates were used as sedative-hypnotic drug for long series of time. The new types of drugs were synthesized in the mid of 20^{th} century. Among them, benzodiazepine was the chief sedative-hypnotic drugs. The minor class of sedative hypnotic drug was tranquilizers. In the first half century, the extensively used drug as “Sleeping Pills” name was barbiturates. These barbiturates were also used during psychiatric examinations for the effect of reducing voluntary inhibition. In the 1950s, the use of barbiturates was declined because of benzodiazepines development. Benzodiazepines become superior to barbiturates for the reducing danger of any tolerance, dependency and addiction. Moreover, the central nervous system is depressed less injuriously by benzodiazepines at higher dose comparing with barbiturate to get the desire effect.

1.3 Classification

Other than benzodiazepine and barbiturate there are other groups of sedative hypnotic. These drugs are called miscellaneous agents for example carbonates, alcohols and cyclic ethers. These miscellaneous are still used. There are some new drugs, for example anxilytic buspirone, melatonin agonist and orexin antagonists are widely used for sleep disorder. Zolpidem, zalaplon, eszopiclon are anxilytic buspirone drugs. These drugs have distinctive characteristics.

The sedatives-hypnotic drugs classify as:

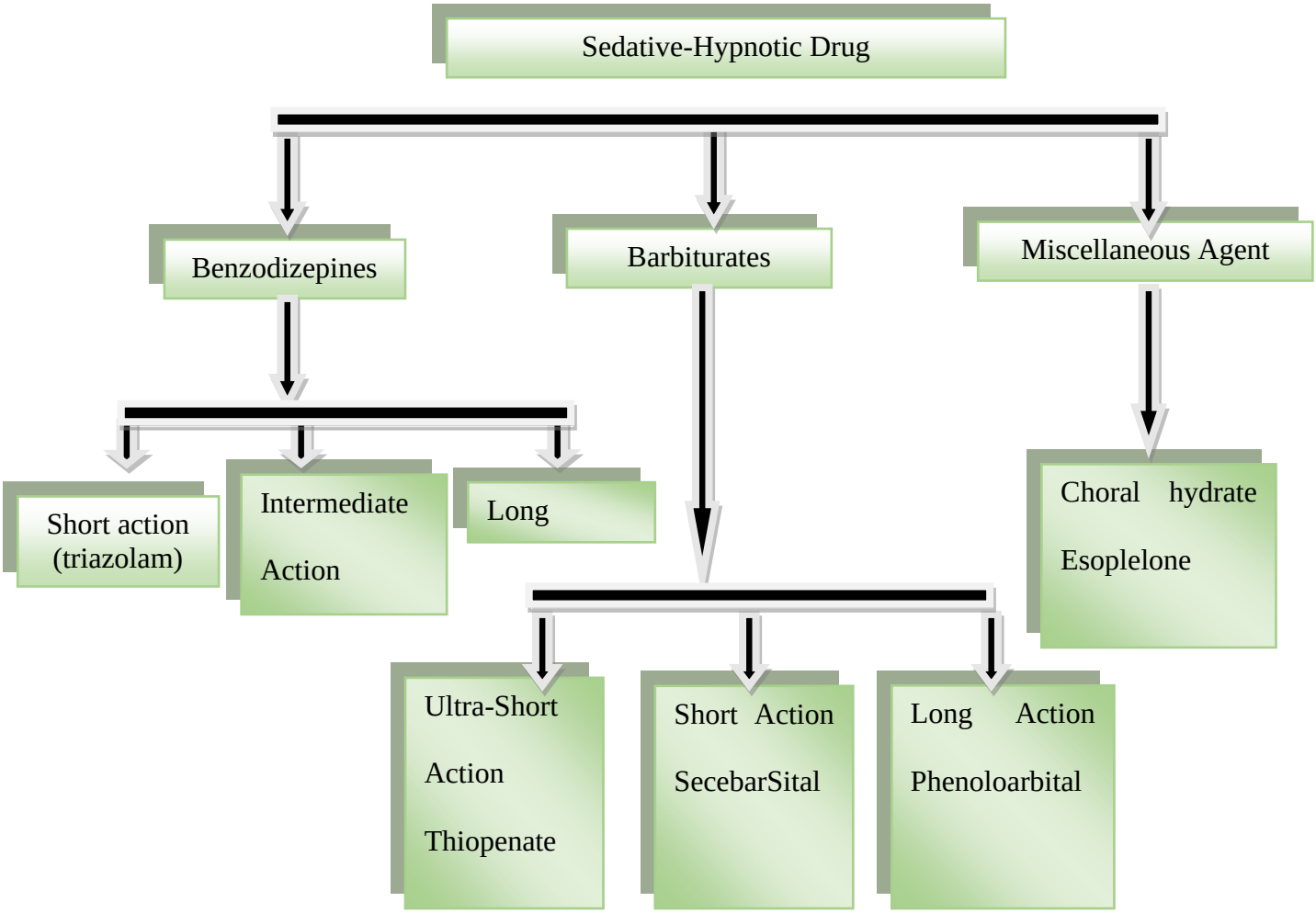

Figure 1: Classification of Sedative-hypnotic drugs

Miscellaneous agents classify as:

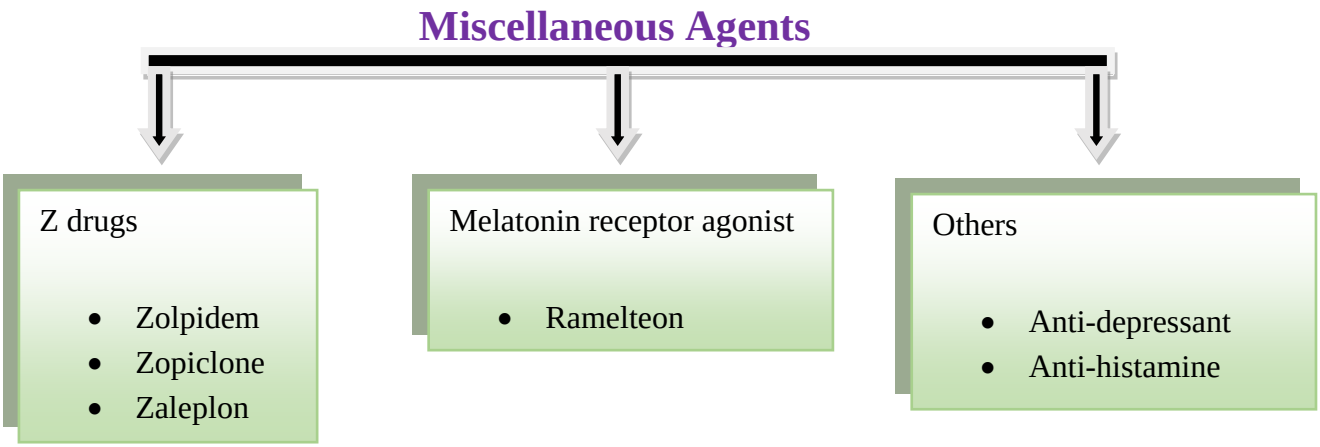

Figure 2: Classification of Miscellaneous Agents

The benzodiazepines class of drug further classified based on indication:

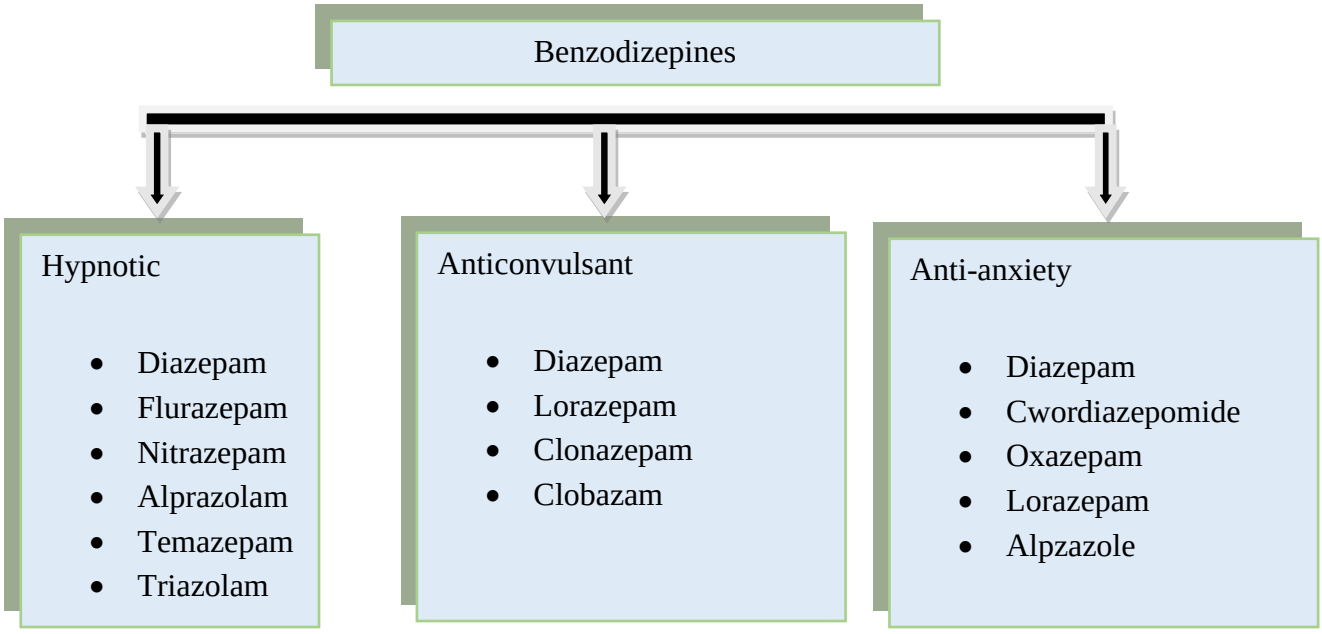

Figure 3: Classification of Benzodiazepine Drugs

Basically the sedative-hypnotic drugs shows different type of action based on the dose is used. For example, at low dose, the drugs show sedative effect or sedation action. At high dose they show sleeping effect or hypnotic action. At higher, these drugs shows Anesthesia effect. In addiction these drugs may lead to coma and death accordance to increasing the dose. Dose dependent action of sedative-hypnotic drug:

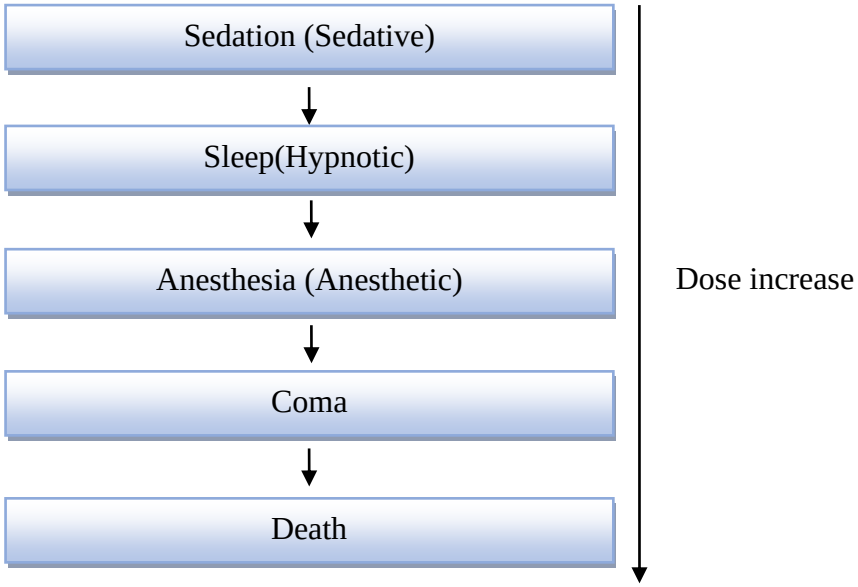

Figure 4: Action of Sedative-hypnotic drugs (Tiwari, A. (2015, February 26). Sedative Hypnotic. Retrieved from https://www.slideshare.net/drashutoshtiwari/sedative-hypnotic-45187755)

Most sedative-hypnotic drugs basically affect central nervous system which is acted in neurotransmission process by passing some step. The drugs work as influencing the neurotransmitter by pre-synoptically. They influence the production, termination, storage and release of neurotransmitter. Moreover, these drugs also work by inhibiting the reuptake mechanism of neurotransmitter which is done by blocking postsynaptic receptors. There are two types of neurotransmitter. One is excitatory neurotransmitter and another is inhibitory neurotransmitter. Based on the nature of neurotransmitter, the action becomes different. Sedative-hypnotic drugs work through GABA receptor. GABA is inhibitory neurotransmitter which is stand for Gama Amino Butyric Acid. GABA receptors are mainly composed of a combination of 5 different sub units. They are alpha beta gamma. These sub units span the

post synaptic membrane. The alpha amino Butyric acid binds with the receptor which triggers an opening path for central ion channel. The ion channel allows the chloride ion to influx. For in fluxing of chloride ions hyper polarization occurred in the neuron which result inhibit the action potential formation. These lead to decreased neurotransmission, causes CNS is depressed. Barbiturate actually works by increasing the duration of opening the chloride ions. On the other hand, benzodiazepines increase frequency of opening of chloride channel. In contrast alcohol inhalation of anesthetic propofol directly opens the chloride ions channel.

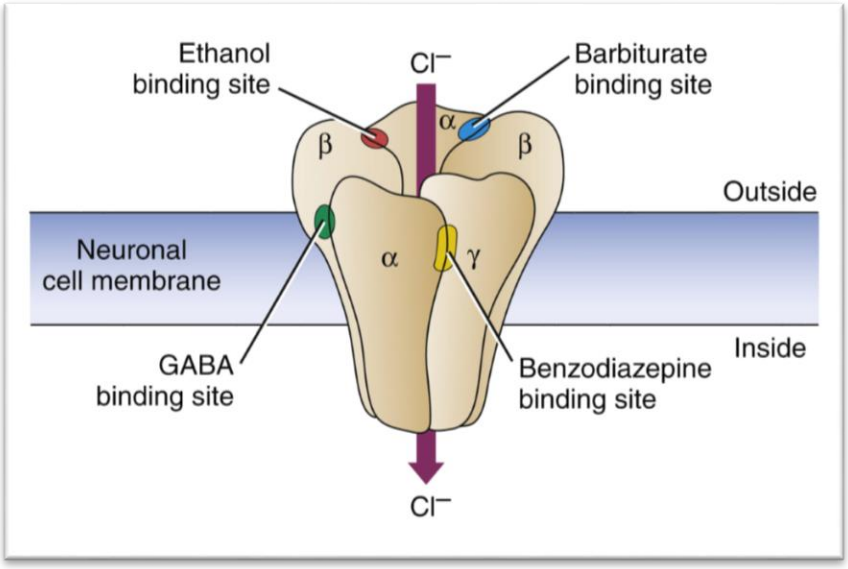

Figure 5: Mechanism of action of sedative hypnotic (Tiwari, A. (2015, February 26). Sedative Hypnotic. Retrieved from https://www.slideshare.net/drashutoshtiwari/sedative-hypnotic-45187755)

A flow diagram of mechanism of action is given bellow:

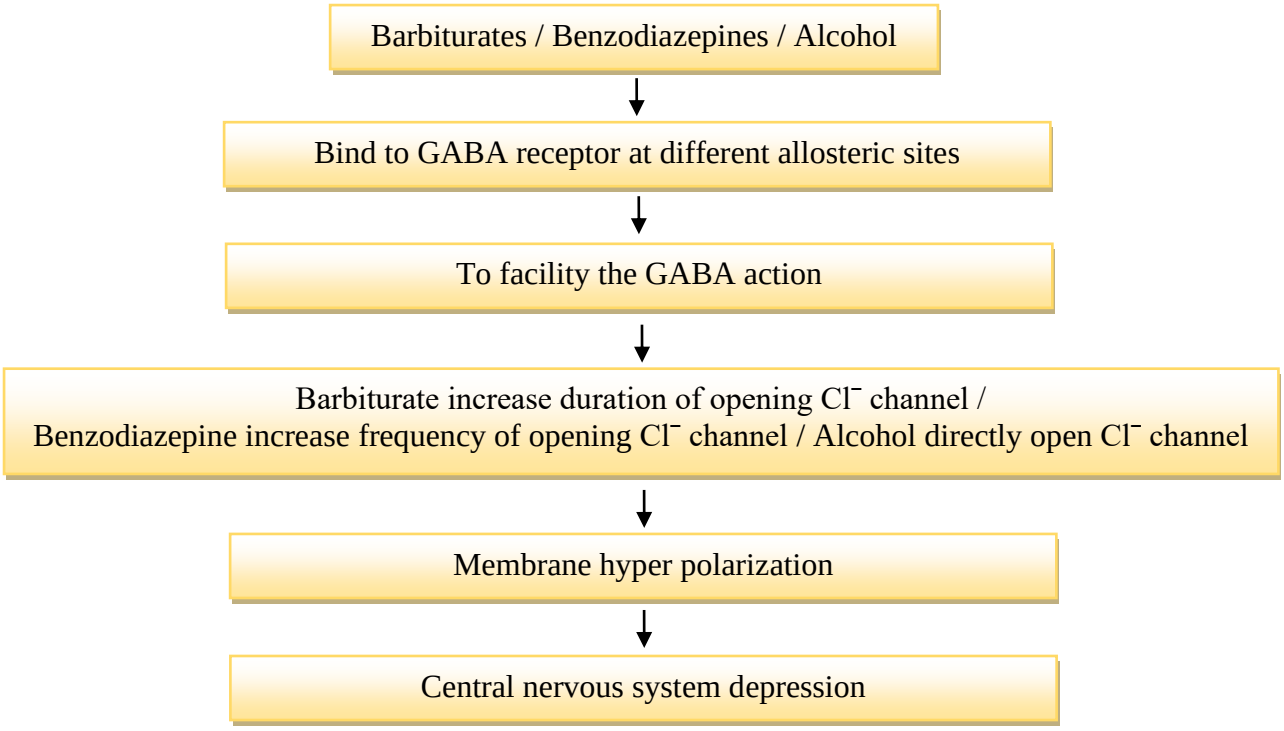

Figure 6: Mechanism of action of Barbiturates, Benzodiazepine and Alcohol (Tiwari, A. (2015, February 26). Sedative Hypnotic. Retrieved from https://www.slideshare.net/drashutoshtiwari/sedative-hypnotic-45187755)

Moreover, through neither selective nor epinephrine reuptake inhibitor some drug show there effect. Here, the drugs bind with the receptor post synoptically which are responsible for reuptake the neurotransmitter. For the binding of drugs, neurotransmitter cannot bind with the receptor. For this causes reuptake is not occurred. These types of drugs are prescribed with the combination of benzodiazepine. For example, busipirone shows action through serotonin reuptake inhibition. SSRI drugs are prescribed for the patient who has chance of addiction or drug dependency. SSRI or SNRI drugs become first line of treatment because it has lower potential for physical dependence. On the other hand, benzodiazepine are barbiturate have more potential for physical dependence then SSRI or SNRI drugs. Moreover, busipirone is used for chronic anxiety and generalized and anxiety disorder.

1.4 Therapeutic effects and side effects

Therapeutically benzodiazepine is used for anxiety disorders; sleep disorder, premedication for anxiety-provoking and unpleasant procedures such as dental surgery, endoscopy and angioplasty. In addition, for seizures treatment, muscular disorder benzodiazepine is used. Basically for skeletal muscle spasms, multiple sclerosis benzodiazepines is used. It is lipophilic in nature and absorbed rapidly after oral administration. Therapeutically barbiturate is used as anticonvulsant sedative-hypnotic an anesthetic drugs. Moreover, Phenobarbital is used for epilepsy treatment on the other hand thiopental is used as anesthesia. Both benzodiazepine and barbiturate have drowsiness side effect which is very common. Other than benzodiazepine have confusion ataxia early morning insomnia, day time anxiety side effect. In contrast, barbiturate causes respiratory depression occurred which may lead to death. Secobarbital, amobarbital, pentobarbital and Phenobarbital were the most commonly prescribed drugs for psychiatric patient as well as sedative and hypnotic drugs. These types of drugs are also used as general anesthetic because these drugs having the capability to produce a deep unconsciousness. For general anesthesia these drugs are used as higher doses. In contrast, at higher dose barbiturate depress nervous system and respiratory system extensively which may lead the patient to coma, respiratory failure and death. In addition the long time use barbiturate may lead to tolerance. In which the patient needs more amount of drug for treatment where having the chances of drug addiction. Moreover, the barbiturate precipitates withdrawal effect which shows some symptom like restlessness, anxiety, weakness and convulsion. Barbirate also produces sleep disruption which was observed by analyzing electroencephalographic patterns (EEG).

1.5 Rationale of this study

The aim of this project is to find out the adverse effects and additional therapeutic effects of sedative-hypnotic drugs. This study was done on different types of people (adult, older adult, pregnant women, male, female) to evaluate the adverse effects individually. Also, find out another drug which has less adverse effect comparing to commonly use sedative hypnotic drugs.

Chapter 2

Results and Discussion

The abuse liability of ramelteon a noble hypnotic and sedative adverse effects

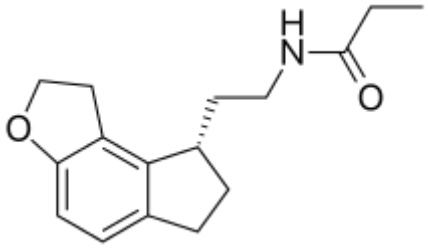

Figure 7: Ramelteon

The purpose of this study is to examine the potential for subjective effects abuse and motor and cognitive impairing effect of ramelteon compared with a classic benzodiazepine (triazolam sedative hypnotic drug) (Johnson et al., 2006)

Main Therapeutic effect:

The article shows that. The principle affect of ramelteon, is improving sleep disorder in older adults and adults patients, who are suffering from chronic insomnia.

Assay Method:

For this study, about eighteen to sixty years old healthy men and none lactating and non pregnant women were participated as subjects. Moreover, the participants were not having any kind of current psychiatric or clinically significant medical condition. In addition, the subjects one year's dependence, nonmedical sedative drug use, active substance abuse were reported. During clinical or physical laboratory evaluations, the subjects were shown abnormal findings were not include in the study. Before beginning the study, the participants were paid.

The double-blind crossover method was implemented to conduct the study. Approximately for 18 days, the researcher subjects were settled in a 14-bedresearch unit. The subjects were given a diet without containing any caffeine before few days of starting the study. Also, the same diet was followed throughout the study. In contrast, the subjects were allowed to smoke cigarettes or tobacco but not during the experiment procedures. The subjects were reciting ramelteon as an investigational drug. During the experiment placebo, sedatives, muscle relaxants, antipsychotics, weight loss medications, anti anxiety drugs were also tested as the research staff and subjects were instructed. For the experiment, the subjects were instructed to take low fat meal about 1.5 hours before administration of drug. The investigated drug was administrated at 8.45 AM. Before 0.5 hours of administration, the subjects were assessed. Moreover, after drug administration the subject were assessed repeatedly for 24 hours. The time was allocated for experiment was 6.45 AM to 5 PM. Before first session, no placebo was administrated to the subject because it was the practicing period for adaptation to procedures. Except weekends and holidays, the session was continued every day. For first and second day the subjects were administered 3mg of alprazolam (commonly abused sedative drugs) with placebo. In addition, next day questionnaire was also done. After that, for 7 session days double-blind method was applied to the participants. Here, placebo, 16mg ramelteon, 80mg of ramelteon, 0.75mg of triazolam, and 160mg of ramelteon were given randomly. After this session, a final session was designed where drug vs money choice procedure were followed. In final session, 0.25mg triazolam capsule, 16mg and 32mg ramelteon table and microcrystalline cellulose 180ml of solution as placebo containing were given. Here, 5 tablets, 3 capsules were administered in each session.

Before 0.5 hours of administration, to subject cognitive, motor performance measure and observer rated were assessed. After administration monitoring was done according 1, 2,3,4,6,8,12 and 24 hours.

Subject-Rated and Observer-Rated Measures: Subject-Rated and Observer-Rated Measures related questionnaires were done in a desktop computer.

Subjective Effect Questionnaire and pharmacological Class Questionnaire: The Subjective Effect Questionnaire contained 2 parts and pharmacological Class Questionnaire asked subjects to categorize the drug effects.

Next-Day Questionnaire: About 24 hours later of drug administration, Next-Day Questionnaire was done where previous drugs effect were asked.

Outcome: For this study, 15 adult were participated. Among them, women were 1 white and 2 black and 12 white were man. The mean age was 28 years and mean weights were 77kg. Moreover, eleven participates were use tobacco cigarettes regularly as reported. In time course of drug effects, Triazolam produced significant dose related and time related effect in orderly.

In subjected rated measure, Triazolam having significant differences comparing with placebo. The triazolam shows potential for abuse and typical effects at sedative drug. For motor and cognitive measure, the triazolam dose significantly scored low.

In another article the effectiveness and safety of Ramelton in older adult is studied. The Ramelton is a melatonin receptor against.(Roth et al., 2006)

Assay Method: For this study, 829 patients were participated and their age was 65 years or above 65 years. Among 829 patients 341 were men and 488 were women. In addition, participates were selected, who already had gone through primary insomnia diagnosis. This can be defined as statistical manual and diagnostic mental disorder. Moreover, the participated patient could not suffer from any significant psychiatric or medical disorder. Also, they were not allowed to take any medicine which affected sleep and wake function or the central nervous system.

The study was conducted for 7 week. These 7 weeks were divided in five periods for evaluation. The first period was for screening test. The second period was for single-double placebo. The third and fourth periods were accordingly for double-blind treatment and single-blind placebo run-out. The last period was for final visit. For the screening period, physical examination, electrocardiography (ECG) and laboratory tests were performed. Some patients were taken placebo for seven nights consecutively. Actually, they were participating for the period of single-blind placebo lead-in.

After, completion of first period the patients were evaluated again for second period experimentation. The eligible patients were randomly given placebo, ramelteon 4mg and 8mg ramelteon as double-blind for 5 weeks and 35 nights. The patients were instructed to record the sleep time after taking medication.

Moreover, the patients were also instructed to take the medication during bedtime. At every visit the patient's adverse events and vital signs were measured. Following second period patients were entered placebo, run-out period for 7 nights. This period was done for evaluating the withdrawal effects and rebound insomnia.

For sleep diaries, everyday's sleep time, sleep quality, total sleep time were reported. A three point scale was for evaluating sleep fully back case. On the other hand, a seven point scale was evaluated for sleep quality.

For evaluating withdrawal symptom of benzodiazepine, questionnaire was done. For all patients the inventory were completed which were done based on illness, side effects, therapeutic effect and global ratting statistical analysis was done using SAS 8.2 version.

Outcome: Among 829 participate patients, 128 participate were discontinued the study. For the efficacy, statistically, there was no significant treatment difference. The effectiveness of ramelteon was improved comparing with placebo. For rebound insomnia, the patients were

evaluated for seven nights. The latency was developed when 4mg ramelteon was given. The total 454 patient among 829 patients, the significant adverse effect was not observed. The adverse effect reported was less than three percentages. The common side effect occurred for ramelteon were headache and dizziness.

Risk of falls in older men occurred due to taking non-benzodiazepine sedative and hypnotics drugs.

Non benzodiazepine sedative and hypnotic drugs also called “Z” drugs. For example zolpidem, eszopiclone. Zaleplon etc. These non-benzodiazepine drugs work through GABA (gama amino butaric acid) receptor same as benzodiazepine.

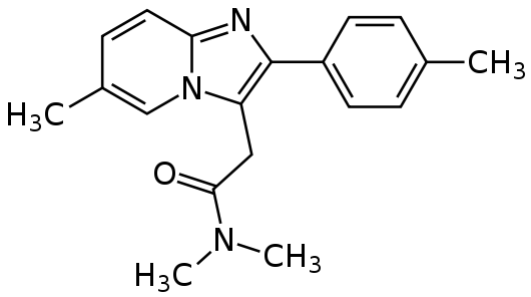

Figure 8: Zolpidem

The purpose of this study was to examine the risk of falls at non-benzodiazepine sedative and hypnotic drug as well as compare risk of falls with benzodiazepine sedative hypnotic drugs in older patient. (Diem, 2014)

Main therapeutic effects: Non benzodiazepine sedative hypnotic also called ‘Z’ drug. For example zolpidem, eszopiclone, zaleplon are used to treat sleep disturbances and preserve architecture of normal sleep. These drugs also work through GABA receptor as benzodiazepine.

Assay Method: For this study, the procedure is done base on medication use, ascertainment of falls, questionnaires and statistical analysis. For this study, the participants were chosen at least 65 years old man.

The baseline examination was done in the participants, who were suffering from prospective osteoporotic fractures. For medication use, the participant's previous medical history and all prescriptions were collected. In addition, all the information of the patients were recorded and matched with the present situation. On the other hand, the non-benzodiazepine and benzodiazepine drugs used participant were differently categorized. Again, they were monitored and reported for last 30 days.

In ascertainment falls, the participants were required questionnaire at 4 month intervals to know the times of falling. The participants who were not able to continue the questionnaire were followed up by telephone. In the present study contain, fall reports of one year period by following 3 examination of subject's visit.

Moreover, other measurements were also considered for this study for example, smoking status, alcohol use, difficulty in daily regular activities. In addition, physical performance was measured by walking speed and chair stand time. These examinations were scored between 0 and 5. By the tiny modified Mini-mental state examination, cognitive function was examined. Here maximum score was 100. In this examination, patient's depressive symptoms selected co morbid conditional (diabetes, stroke, pulmonary disease, angina, congestive heart failure) were evaluated. By GDS (geriatric depression scale) mental depression was examined. Additionally, body weight was calculated with a balance beam scale. On the other hand, height was measure by a wall-mounted Harpenden stadiumeter. Finally, body mass index was measured in kilograms per square meters.

Lastly, statically analysis was done. In statically analysis, comprise of non-benzodiazepine and benzodiazepine medication was done. In the primary analysis, the relative risk (RR) was estimated by Poisson models, log binomial, medication use and risk of falls. About, 95% confidence interval (CI) among any falls and recurrent falls with nonuser by medication take category as the referent group. Explorations of history of fall and medication infraction were done. The secondary analysis conduction was limited within 2722 men, who had the data of self-reported sleep quality from Cartier sleep examination. All statistical analysis were performed through SAS software version 9.1

Outcome: Among 4450 participant, 94 men reported about the use of non-benzodiazepine drug. 81 men use zolpidem, 3 men used zaleplon and 10 men used ezopiclone. On the other hand, 177 participants were reported to use of benzodiazepine drug. In the age-adjusted models, recurrent falls were associated with non-benzodiazepine use. Here, for an increased risk falls the RR value 1.44; 95% CI 1.15, 1.81. On the other hand, recurrent falls RR 1.51; 95% CI 1.07. 2.14. The non-benzodiazepine user having greatest impact with GDS and the risk of falls was RR 1.30; 95% CI 1.07, 1.58. The PSQI is significantly unchanged in the result. The estimate relative risk of recurrent fall for the age-adjust is 1.77; 95% CI 0.83, 3.79

In contrast, the benzodiazepine use associated with recurrent falls (RR) 1.40; 95% CI 1.06, 1.85 and increased risk of any falls RR 1.35; 95% CI 1.12, 1.61 showed in age-adjust model. The evidence of interaction between benzodiazepine take and history of falls was not proved. From this studies result it can be said that the non-benzodiazepine drugs have more chance to risk of falls in older mean than benzodiazepine.

Indiplone is a non-benzodiazepine sedative hypnotic drug which has effect of anti-aggregation on platelet.

This study tries to activate A2A receptor for indiplon which developed as a drug for insomnia treatment and analyze the effect on platelet through in vitro activity. (Burgos et al., 2019)

Main therapeutic effect: This drug is mainly developed for insomnia treatment.

Additional therapeutic effect: In this study shows, Indiplon can inhibit platelet aggregation through A2A receptors was investigated.

Assay Method: The chemical were used for this study were, Dimethyl sulforide, Aderosine 5-diphosphatebis, pyrazolo, Indiplon. For flowing of antibodies eytometry anti-CD62P-PE and anti-CD6I-FITC were purchased. By using the human adenosine A2A receptor structure, docking protein-liy and was conducted. In 2INC database the indiplon structure was available. The initial complex was formed with using a receptor grid which is located on amino acids which create site for adenosine binding. By Gude prediction was aggregated by using extra precision configuration, which includes post-docking minimization and cigand flexibility. In addition, for evaluating software accuracy, a docking use adenosine structure was performed for rebutting the complex with the receptor. By performing same structure energetic parameters and structural analysis was done of A2A Indiplon. For, predicting a theoretical cgbind an energy calculation MM-G6SA was done using prime. MOLE online was used for analyzing the tunnels observation in the A2A structure. By using pyMol all image were created.

For performing human washed platelet suspensions, platelets were collected from 6 healthy participants. In a citrate tube (3.2%, 9.1v/v) various blood were collected. The sample was centrifuged for 10 min at 240g for getting platelet-rich plasma (PRP). Then the PRP was adjust to concentration of 200 to 300 x 10^9 platelets/L. Then for washed platelet proceeds the

centrifuge was done for 10min at 650g and platelet was washed with HEPES tyrodes buffer which contain PGE1. For each assay each volunteer were independently processed.

After that platelet aggregation assay was done using a lami-aggregometer. By passing light Trans mission according to cross and born. For aggregation test, at 37 C PRP were incubated for 3 min. Then two antagonists 2M241385 or MSX-2 were added for investigation of aggregation. The effect of Indiplon on aggregation was reported for 6 min. By using modi tying methods from there on, p-selection surface expression was obtained. For this the PRP was incubated as previously. 5000 events were acquired for pen conditions and all analysis development done by using Accuri C6 software.

Statistical analyses were done through Graphpad software (version 6.0). Data empresses as mean standard error all measurements performed in six separate platelet donors.

Outcome: In docking performance Indiplone being a ligard able to procuce stable intraction with the A2A receptor. From this, it can be indicate that Indiplone can interact with AA receptor both structurally and engertically in favorable manner. The indiplone show decrease aggregation percentage to 23.6 ± 1.2% which is almost 70%. Indiplone inhibit aggregation with ADP based the concentration is given.

In P-selection expression the aggregation of platelet inhibit 73.8 ± 2.7% and 58.5 ± 1.1%in two different concentration of indiplone (500 and 260). On the other hand,by the 2M241385 the inhibition of aggregation using indiplone was 70.4 ± 0.8%. This result indicates that the indiplone having good effect for prevent aggregation of platelet.

To examine the sedative and hypnotic effects in mice by using pinelliae Rhizoma praeparatum Cum Alumine exatraction.

The purpose of this study was to investigate sedative effect of PRPCA's exatraction through locomotor activity test and find out the most effective concentration for those effects.(Lin et al., 2019)

Extracted compound: From this study, the extracted compound was 32 in total. Among these compound 19 Alkaloids, 3 volatile oils, two fatty acid and two phenylpropanoids were identified.

Assay Method: For this study, the experiment was designed in three parts. Firstly, to investigate the sedative effect in mice and the proper dose of PRPCA was identified. Secondly, to investigate the hypnotic effect and promotion of sleep in mice by PRPCA.Finally, to identify the chemical compounds present in PRPCA. For this study, the drugs and reagents were used, dried tuber of Pinellia Ternate processed with an adjuvant material called Alumine, diazepam, sterile water for injection, grade acetonitrile for high performance liquid chromatography and ultra pure water as aqueous solution. For preparing the extraction, each bag of 0.5g of PRPCA granules were dissolved in SWFI. Here 4.5 bag, 9 bags, and 18 bags of PRPCA was titrated to 60ml solution. The yield concentration was 0.45g/ml, 0.98g/ml and 1.8g/ml accordingly. For storage of solution, temperature was maintained below 4c. For diazepam solution preparation, tablets of diazepam were dissolved in 25ml of SWFI for obtaining 0.1 mg/ml of liquid diazepam. For chromatography the crushed granules of PRPCA were soaked in cold acetonitrile overnight. For extraction, these were subjected to 45 min for ultrasonification. The extract was centrifuged for 10 min at 10000n/min and supernatant was filtered through 0.22 micro porous membranes. Finally stored at -80 °C. For sedative test, 20- 25 g of 30 mice were divided randomly among 5

groups. For sleep monitoring 18 mice were divided randomly into 3 groups. For locomotors test, different concentration of PRPCA was given for finding the most effective concentration and sedative effect. Each mouse was placed above 17.5cm from the container. To record mice movement, behavioral recording all detectors were connected. For 24h, in the containers the mice were habituated. The drug was administrated intragastrically at 7pm for 14 days. Moreover all data were collected through computer for 14 days in every 5 min. The data were summed up after 24h. For sleep test, 0.45g/ml PRPCA in one group, SWIF in one group and 0.2mg/Ml DZP as control in one group were given. For 14 days the drugs were given and simultaneously the mice's electroencephalography (EEG) and electromyography (EMG) were monitored. In addition, the wakefulness, rapid eye movement sleep, non-rapid eye movement sleep was monitored. For chromatography and mass spectrometry analysis liquid chromatography system and a quadruple time of flight spectroscopy were used. Here, water was used as mobile phase and acetonitrile used as phase B.Temprature of colum was used as40C.Elution was followed as 5-95%. The injection volume was 2 micro litter and flow rate set as.0.4 ml/min.

ESIin is set as parameter for both the posetive and negative ionization modes. Helium (He) and pure nitrogen were used as collision gas and nebulizing gas. The voltage were used according to capillary ESI voltage +3000v, capillary ESI voltage - 2500v, cone voltage 40v, cone gas rate 50 l/h dissovation rate 800. For statistical analysis, by the mean+ and mean - the standard error of the mean all data were expressed. Statically analysis, locomotors activity data, sleep monitoring were assessed by using SPSS 19 version.ANOVA and wayANOVA. For comparing among groups least significant difference method was used. During P values<0.05 was considered.

Outcome: For sedative effects of PRPCA in mice locomotors activity test result were given in table

Table 1: Impact of time and group on locomotor activity in mice

	F	P
Time	2.133	0.088
Group	4.267	≤0.001
Time*Group	6.242	0.004

From days 8 to 14 significant difference were observed at the same time among the groups.Comparing locomotor activity for PRPCA group1 showed lower activity than other four groups from day 1 to day 14. The p values were p<=0.001,p=0.012,p=0.010 and p=0.027.Here the comparison was done among DZP PRPCA's different concentration and SWFI. For sleep analysis PRPCA showed the increased sleep and decrease wakefulness in mice. The result was taken based on frequency and amplitude from EEG/EMG analysis, NREM sleep and REM sleep. The hourly wakefulness time 46.30% at 9am. Also, PRPCA decreased the number of bouts of wakefulness, where duration was 16-32s and 32-64s. The percentage was 38.91% and 31.68% accordingly. On the other hand diazepam decreased bouts of wakefulness 35.09% and 33.33% accordance to the same duration, where, the difference was not much variable. From the result, this study showed that, the PRPCA extraction give similar effects like diazepam. On the other hand PRPCA extraction has fewer side effects than DZP. so the extraction may be the safer use for patient.

Older adults who are receiving hemodialysis psychoactive medications and their adverse outcomes.

To investigate the association into the psychoactive medications use and hospitalization for altered fall, mental status and fracture into hemodialysic older patients.(Ishida et al., 2019)

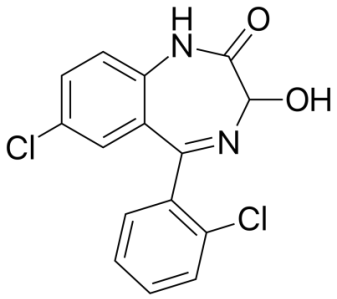

Figure 9: Benzodiazepine

Assay Method: This study was done by using cohort study. Where the data of 'clinical and prescription drug were collected from the US rental data system (USRDS). This study was only done on the hospitalized patient. They are 65 or more over 65 years old. The participant were excluded from the study if they were died, loss of follow-up, with drawl from dialysis or change to other dialysis modality and recovered function. This participant must receive hemodialysis for chronic maintain.

This study was done basically on the anti-cholinergic anti-depressant particularly. In the psychoactive medication exposure, the exposure periods were the time of starting of date of a prescription’s service plus the number of supplied drugs.

The outcome variables were on mental status, fracture (hips, pelvis, leg, foot, femur, arms or skeleton fracture). The information were collected from CPT (current procedural terminology) codes from the revenue, Instructional claims files and physician/supplier.

The statistical analysis was done in different two groups, one was who were taking psychoactive drug and another group was who are not taking the psychoactive drug. There

different types of disease was observed (For example cerebrovascular disease, eplepcy opioid dependence etc) percentage value.

Outcome:

This study showed anti-cholinergic anti-depressant exposure was significantly altered mental status at highrt hazard. The hazard ratio 1.24; 95% and confidence internal was 1.02-1.50. On the other hand shorter duration sedative-hypnotic drug showed higher hazard (HR = 1.20; 95%) than longer duration sedative-hypnotic drug.

In another article also reported about the adverse effects of benzodiazepine in older adults. This study was done by a population based retrospective cohort survey. The study had done the survey to find out hazard effect of benzodiazepine on respiratory track on older adult. The data were collected from large eight Ontario provincial health administrative databases. Securely the databases were held in a de identified from. After that the data were analyzed. Moreover for this study medication report's record were collected from Ontario Drug Benefit. This data were contained all out patients drug dispensed time, supplied days etc. For this study the collected about 65 years old patient's data. Data were also collected from Ontario Mental Health Reporting System, National Ambulatory Care Reporting System, and Registered Persons Database.

In this article, the result were given as, the new benzodiazepine user showed higher risk for respiratory execration (RR 1.4; AR 1.51%, 95% CI 1.36 to 1.54). On the other hand for the emergency patients(pneumonia) the risk were (RR 1.92; AR 0.68%, 95% CI 1.69 to 2.18). In contrast, the non benzodiazepine user showed less risk for respiratory execration. The risk was (RR 1.02; AR 0.17%, 95% CI 1.00 to 1.20). To compare the benzodiazepine user's result with non benzodiazepine user's it was cleared that benzodiazepine cause high risk to respiratory disease.

To examine the hypnotic effect of rare protopanaxatriol-type and protopanaxadiol type ginsenosides.

The purpose of this study was to find out the hypnotic effect on protopanaxatriol type and protopanazadiol type ginsenosides. In addition,find out their another therapeutic effect.(Mou et al., 2019)

protopanaxatriol type and protopanazadiol type ginsenosides, which is a major active component of ginseng.

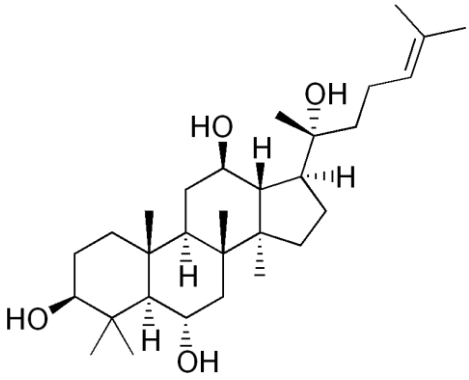

Figure 10: Protopanaxatriol

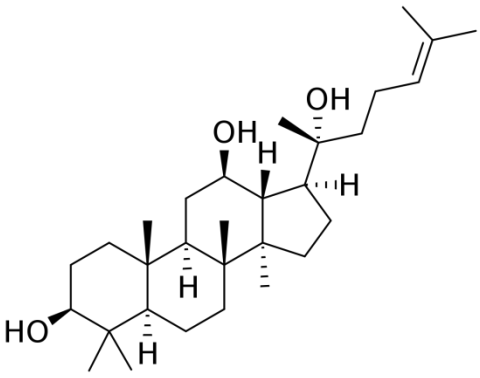

Figure 11: protopanazadiol

Main therapeutic effect: Regulate central nervous system and exert protective effect on neurons

Additional therapeutic effect: Anti-inflammatory anti diabetic and cancer chemoprevention.

Assay Method: For this study 60 adult mice were taken with the weight 20±2 g. The temperature and humidity maintained 24-26 °C and 55±5% accordingly.

The mice were randomly divided into 6 groups for the experiment. The drugs andmeterials were used for the study, ginsenosides, 5-hydroxy tryptophan, flumazenit, p-chlorophenyl-alarine, caffine and Phenobarbital.

For HPLC (High Performance Liquid Chromatography) the girosenoside were added with the citric acid for 3 hours at 80-100°C and 60-80°C neutral pH were maintained. Here C18 column and 203rm were used. Acctoritrile and water were used as gradient elution solvent at 50:50 and 60:40.

Sodium pentrobarbital dissolved in saline (0.1 ml/log) and injected intraperitoneally protoparaxadiol-type ginsenosides dose were 64 $mgkg^{-1}$ as low dose and 96 $mgkg^{-1}$ as high dose. Protoparaxatriol-type ginsenosides dose were 64 $mgkg^{-1}$ as low dose and 96 $mgkg^{-1}$ as high dose. The ginsenosides were given intragastrically before 30 minute sodium pentobarbital administration. A insomnia model was design by caffine. Herecaffine was given 0.5 hour before rare ginsenoside and sodium pentrobarbital. The control grouped was only giving solution. For this study, single dose was used.

Behavioral analyses were done by Inner-field behavior test. To adjust the new environment, mice were adapted for 5 minute, the locomotion activity test were done after 30 minute of drug administration. Activities were measured within 5 minute. To evaluate ginsenosides sedative and hypnotic activity, the locomotion time, number of rearings and locomotion distance were used as indicators.

Perotobarbital-induced sleep test were done between 8.30 and 11.3 a.m. Here, righting reflex, disappeared, indicative of sleep, sleep latency were recorded. Sleep duration was also recorded.

All data were expressed as the mean ± standard error of mean and experimental data were analyzed statistically by the SPSS220.

Outcome: Through HPLC the main component of rare PD and PT ginsenosides were identified. In PD ginsenoside, S-Rg3 (28.57±0.27%) Rk1 (22.19±0.26%), Rg5 (22.16±0.68%) and R-Rg3 (26.74±0.47%) found as main component. In PT, Rk4

(49.08±0.26%) was highest as main component and other component were Rk3 (24.05±0.09%), R-Rh1 (16.44±0.56%)

The sedative hypnotic effect was observed by locomotion activity. Here, the high dose DP (96 $mgkg^{-1}$) were significantly decreased the locomotion activity ($p<0.05$). On the other hand, PT showed effective result for both lower dose and higher dose ($p<0.05$). For comparing the sedative and hypnotic effect, a sub-hypnotic dose of sodium pentobarbital were used, where the p value of pentobarbital showed ($p\leq 0.05$) at 32 $mgkg^{-1}$ and $p<0.01$ at 48 $mgkg^{-1}$ which was similar to PD and PT ginsenosides. For insomnia a caffine model was designed. During this model, PD and PT ginsenosides increased the duration of sleep and reducing sleep latency. During PCPA induced insomnia in mice 300 $mgkg^{-1}$ P-chloroprene lalarine can causes complete insomnia in mice within 24 hours. Here PD and PT ginsenoside showed effective result through shortened sleep latency ($p<0.001$) and prolonged sleep duration.

Phenobarbitals effect on sleep and nighttime cortisol and growth hormone levels.

The purpose of this study was to determine the acute and chronic effects Phenobarbital at low dose. In addition to find out the withdrawal effect of Phenobarbital on plasma GH and cortisol patterns at night. (Prinz et al., 1981)

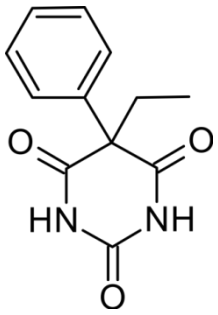

Figure 12: Phenobarbital

Assay Method: 5 healthy adult male were worked as volunteers for this study. Their ageds were 21 to 25. They were instructed to maintain sleep time, did not take any medication and alchohol during the experiment.

The subject were given placebo on the base line night, for 9 night Phenobarbital (100 mg) were given and finally for withdrawal effect one placebo was given at last night. They were slept n laboratory for 3 base line night and foingt drug night. From 5 to 10 night they slept at home. Again from 11 to 13 night they slept at laboratory. In the first baseline night and 11 night the subject were attached with EEG electrods and a sham venous cannula.

Sleep data were collected at 2^{nd} and 3^{rd} placebo nights. On the other hand, hormone data were collected from night 3, night 4 for acute, night 12 for chronic and night 13 for withdrawal. In addition, day time hormone rhythms also measured between night 12 and 13 and night 3 and 4.

Sleep measure were recorded by following rechtschaffen and kales conventions. The subjects were gone for sleep at their usual time and sleep till they wake up at morning. The sleep measure were coded to make unaware about the experiment.

For hormone analysis blood were obtained from venous at every hour during walking and every 20 minute during bed time. All subjects maintained a regular eating habit. Determination of plasma GH concentration was done through standard radioimmuro assay techniques by utilizing radioimmuro assay material.

On the other hand, plasma cortisol levels were analyzed through competitive protein-binding method. Inter and intra variability for assay was under 10%. If greater 10% was observed, then the assay was done repeatedly.

Outcome: The acute drug nights blood levels of Phenobarbital were showed near the threshold in gas chromatography procedure (5 ug/mL or greater). The peak for chronic night was 6 to 9 ug/ml after 2 to 4 hours of drug administration. Comparing with the placebo,chronic Phenobarbital reduce the latency to sleep but not the acute ($p<0.05$) and Wakefulness ($p<0.1$) in the first half night.

For cortisol level, acute, chronic and withdrawal showed 32.38±5.72, 35.53±5.73 and 35.12±6.77 ug/100ml accordingly. The peak were 8.9+0.86, 12.5±1.56 and 9.4±1.81 for acute, chronic and withdrawal. These result showed that none of the 3 condition alter night cortisol integral values significantly comparing with placebo (35.50±2.75).

For GH level the integral vale for chronic, acute and withdrawal were 8.96±3.46, 7.24±2.17 and 13.84±4.22. Comparing with the placebo (10.79±3.02) acute and chronic reduce the GH levels and withdrawal increase the GH levels at night.

Alprazolam’s effect on post operative pain as a preoperative adjuvant analgesic in laparoscopic donor Nephrectomy patients.

The purpose of this study, to evaluate the analgesic property of Alprazolam in laparoscopic donor Nephrectomy patients by administrating different dose. (Avanaz et al., 2019)

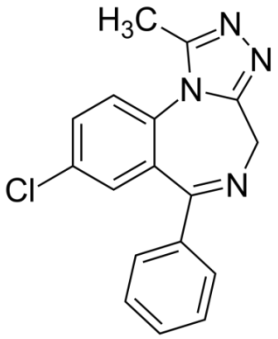

Figure 13: Alprazolam

Therapeutic effect: Treat anxiety, panic disorders, and premenstrual dystrophic disorder in women.

Additional therapeutic effect: Analgesic

Assay Method: For the study, the patients were divided in three groups for different dose analysis. The patient's ages were 18 to 65 years and body mass index ≤ 28 kg/m². Before administered of analgesic verbal pain score (VPS), numeric pain score, ramesy sedation score, body temperature, heart rate, blood pressure, and operation time, postoperative and intra-operative were analyzed.

The first group was administrated 0.5 mg alprazolam, 2nd group was administrated 1mg alprazolam and 3rd group was given no alprazolam. In LPN center the patient were evaluated routinely with RSS, NPS and VPS. Analgesic were administered to the patient who having score of VPS ≥ 2 and NPS ≥ 5. In addition 100mg tramodal and 500 mg paracetamol were infused intravenously which was counted as additional dose analgesic. For statistical analysis IBM-SPSS version 20.0 was used. Continuous variables were specified as median, mean ± standard deviation and categorical variable as a percentage and number. The error margin

was = 0.05. For parametric test 2 independent group's average was analyzed and assumptions were used.

Outcome: In the results, after surgery the additional analgesic administration had not significantly change the RSS, VPS and NPS parameter. In contrast, for systolic and diastolic blood pressure showed significant difference for both group 1 and group 2. In case of systolic pressure, the average change for group 1, group 2 and group 3 were -11.52mmHg (p=.007), -13.56 mmHg (p=.017) and -5.88mmHg (p=.325).In case of diastolic, the average change for group 1, 2 and 3 were -4.92mmHg (p=.131), -8.68mmHg (p=.014) and -1.4 mmHg (p=.674) respectively. In addition for heart rate significant differences were observed. For group 1, 2 and 3 the beats/min were -13.6 (p=.002), -3.36 (p=.313) and -1.88 (p=.654) respectively. For men and women, there was no significant change in VPS, NPS value individually. The values were 4.7±0.67 for VPS and 7.3±1.16 for NPS. (p=.655) VPS and (p=.155) NPS.

In another article it was showed that alprazolam had adverse effect on different dose. This article collected data on adverse drug reaction of alprazolam and analyzed those. The data were collected from Pharmacovigillance report where ADR were reported.

This article showed the result for ADR due to alprazolam were,

Table 2: Adverse effect of alprazolam

>10% (4 mg dose) Drowsiness (41%) Depression (10-15%)
• >10% (10 mg dose) Drowsiness (77%) Impaired coordination (40-50%)
• 1-10% (4 mg dose) Tachycardia (5-10%)
• 1-10% (10 mg dose) Increased salivation (5-10%)

Moreover this study also claimed about gastrointestinal obstruction, hepatic failure ADR due to alparazolam from Post marketing Reports.

To use of benzodiazepine in pregnancy

The aim of this study to find out the adverse effect of benzodiazepine during pregnancy and some solution to treat anxiety during pregnancy other than benzodiazepine. (Marc et al., 2008)

Therapeutic effect: Anxiety and insomnia, Epilepsy

Additional therapeutic effect: Anesthesia for acute agitation.

Assay Method: This study was basically a survey based study where all the data were collected from the national Institute of drug abuse. The survey data were also collected from national survey on drug use and health which was done on 2015. This study analyzed the data and made a discussion on the benzodiazepine use during pregnancy.

Benzodiazepine basically prescribed for anxiety. This study showed from the analyzed data, that women have more chance of anxiety during pregnancy. The chances of anxiety in first trimester about 18.2%, in the second trimester about 19.1% and in the third trimester 24.6%. This study also showed that about 1.2% was prescribed benzodiazepine and 3.9% were prescribed selective serotonin by the analyzed data.

Outcome: By analyzed the data, this study found out some adverse effect of benzodiazepine use during pregnancy. The effects were amnesia, arrest of seizures, short term effect include sedation, fatigue, lethargy, higher doses can lead to dizziness, vertigo, mood swing, visual distortion, confusion, euphoria. The long term effects of benzodiazepine in pregnancy include short term memory loss and cognitive decline.

This drug also caused for the drug dependency showed by the study. In addition, the lethargy was 71.1%respiratory depression was 29.0%, respiratory arrest was 4.5% and cardiac arrest

was 1.9% showed by study from data analyzed. For withdrawal result, at high dose delirium and seizure were begun. The withdrawal effect may show within 24 hours. Moreover, benzodiazepine can cross the placenta which is harmful for the fetus. The benzodiazepine increases the risk of congenital malformations. In addition benzodiazepine causes spontaneous miscarriage, preterm delivery and low birth weight. The odds ratio for preterm delivery and low birth weight were 2.03; 95% CI 1.11-3.69 and 1.55; 95% CI 0.96-2.50 respectively. Moreover benzodiazepine causes poor muscle tone and poor feeding. As it can cross in breast milk causes infants hypotonic, somnolence and apnea.

For solution, the pregnant women can take mind-body intervention, bio feedback; hypnotherapy and yoga fro overcome the anxiety because the benzodiazepine and other anxiolytic medication have sensitivity and most adverse effect during pregnancy showed by this study.

Some other articles also showed adverse effects during pregnancy for using sedative and hypnotic drugs (Benzodizepine, Z- drug). These studies were done through data analysis. The data were collected from Indian Journal of Psychiatry database, Medline, pubmed, Science Direct accordingly. (Cassidy et al., 2012); (Shuster, 1986)

Among These articles, one article reported about the withdrawal effect of common sedative hypnotic drug (benzodiazepine) during pregnancy. It showed that if any pregnant woman took drug more than 3 to 4 weeks and stopped suddenly. The woman showed some symptoms which indicate the withdrawal effects of the drug.

Table 3: Symptoms of benzodiazepine withdrawal

Psychological effects	Gastrointestinal symptoms	Central nervous system exitability
Mood swings, Poor concentration, Dysphoria, Feeling of unreality, Agitation,	Diarrhea, Anorexia, Nausea	Termor, Delirium, Nightmares, Hallucinations, Sensory disturbance in taste, sensitivity to light and sound

This study also showed that seizure would occur due to benzodiazepine withdrawal effects.

In another articles showed that, the benzodiazepine was responsible to increase risk for cesarean delivery.In addition, benzodiazepine also caused for low birth weight and need ventilator support to the neonatal. The study showed the OR for cesarean delivery, low birth weight and ventilator support accordingly 2.45; 95% CI, 1.36 to 4.40, 3.41; 95% CI, 1.61 to7.26 and 2.85; 95% CI, 1.17 to 6.94. (Basu et al., 2003)

In another article showed that the French Pharmacovigilance database reported about serious adverse effects to infants during breast feeding. Infants suffered from somnolence, apnea, and hypnotonia. Moreover , the mother also suffered from delayed feeding and poor feeding.

To find out the adverse effects of other Z-drugs of Zolpidem.

The purpose of this study is examining the adverse effects forusing Z-drugs and Zolpidem as sedative hypnotic medication. (Olson, 2008)

Therapeutic effect: To treat insomnia.

Assay Method: For this study, the method was followed to collect data on z-drugs adverse reaction and analyzed those. The data were collected from adverse drug reactions advising committee (ADRAC). The data were analyzed based on unusual adverse effects, nocturnal activity with amnesia, sleep walking, bizarre and compulsive behavior and hallucinations and psychosis. In this study, comparative incidence of adverse effects and recommendation were also done.

Outcome: This study showed that, about 104 reports had received on hallucination, 62 amnesia and 16 on unusual adverse effects were reported by 2007 in ADRAC. During inappropriate behavior the patient had no memory. In contrast, only for zolpidem about 400 adverse report were reported and up to 14 death were occurred. For zolpidem, the amnesia report frequency was higher than other benzodiazepine. The bizarre behavior was also common in zolpidem use patient. They were taking multiple psychoactive drugs also alcohol with zolpidem. This study also find out other adverse effect for zolpidem, like sleep walking, some compulsive behavior also showed, for example sleep eating, sleep driving also reported.

In addition, zolpidem had been linked with suicide. In contrast, maximum report and database showed that z-drugs have no link to suicide causes poisoning. The most frequent adverse effect reported was hallucination for zolpidem. In older adult patient cognitive and psychomotor related adverse effects were common. The study recommended using other z-drug not zolpidem as it contains more adverse drug effects for managing insomnia.

An in-vivo study for sedative-hypnotic, anxiolytic and anticonvulsant effects by using extract of polyphenol-Rich *thymus kotschyanus*; involvement of GABA receptors showed the evidence.

The purpose of this study was to fing out the sedative-hypnotic, anxiolytic and anticonvulsant effects on mice by using *Thymus kotschyanus* extract a polyphenol work through GABA inhibition. (Jahani et al., 2019)

Extraction of *Thymus kotschyans* a polyphenol compound.

Therapeutic effect: Sedative-hypnotic effect and anxolytic effect.

Additional therapeutic effect: This extract showed anticonvulsant effect.

Assay Method: The aerial part of thymus kotschyans plant was dried at room temperature and crushed as very fine powder through a grinder. By maceration of powder, the metharolic extract was extracted.

For this maceration the plant powder were dissolved 900ml of 96% methanol on a shaker. Here room temperature was maintained. The process was done repeatedly for three consecutive days. For filtration filter paper used and rotary evaporation was done. The extraction yield was 3.5% w/w calculated.

For drug of reagent, extract, pentylenetetrazole diazepam 10 ml/kg, flumazenil 5 ml/kg and pentobarbital were used. The experiment done on male mice (weighted 18±0.25 g) temperature controlled 22±2 °C. According to national institutes of Health (NIH) guidelines, all procedures were conducted. For pherolic content determination, colorimetric method was used with Follin-ciocalteu reagent. Here gallic acid at different concentration (25, 50, 75, 100, 150 and 200 leg/ml; in mentharol) mixed with 5ml of Folin-ciocalteu. After 5 min 4 ml of Na2CO3 was added. Temperature were maintained and incubated for 30 min. By uv-visible spectrophotometer observation was done. Here 400 leg/ml thymus kotschyanus extract were used.

For lavonoid content determination Aluminum chloride was used as reagent. The concentrations were used 25, 50, 75, 100 and 150 kg/ml methanol. Here incubation was done at room temperature for 40 min.

Acute toxicity study was done in different 4 groups. For anticonvulsant activity test pentylene tetrazole and mamimal electroshock were used. Here mice were treated with 50, 200, 400 and 600 mg/kg body weight concentration.

For elevated plus maze test, the plus-maze were placed above 50cm from the floor and same concentration of extraction were used. Pentabarbital induced sleep test were done in 7 groups and the same concentration of extraction were used.

Outcome: The maximum median lethal dose and non-fatal dose were 56838 mg/kg found in acute toxicity study. The total phenolic content found 225.72±12.03 ug/mg and total flavonoid content were found 77.06±4.78 ug/mg.

For anticon vulsant activity, the extract showed protective effect against pentylenetetrazole induced seizures. Anxiolytic activity observed through plus maze and open field test. Here every 10 min observation was recorded and the extract showed positive effect. For hypnotic and locomotors activity test of extract company with pentobarbital and midazolam respectively. Here the extract gives satisfying effect comparing with other drug.

Moreover the extract had less adverse effect than other drug showed in the study. The total distance moved was less at 600mg/kg. Extract in 30 min. In contrast, after 24 hours observation the total distance move was less at 400 mg/kg. During elevated plus maze test, at 600mg/kg give more effective result.

During outpatient colonoscopy, dexmedetomidine using has limited utility to conscious sedation.

The aim of this study was to evaluate the dexmedetomidine's ability for providing sedation and analgesia in colonoscopy outpatient. In addition the outcomes are examined including side effects, discharge readiness and cardio respiratory variable. (Jalowiecki et al., 2005)

Therapeutic effect: It has sedative and analgesic effect.

Assay Method: For this study, single-blind study was randomly conducted among population of patient who were undergoing ambulatory colonoscopy. For this study, 64 patients (aged 18-64 years) were chosen as participant.

The patients were excluded who were pregnant, chronic use of addition psychiatric or emotional disorder. The patients were dividing into 3 groups. In first group contain 19 patients were infused 1 ug/kg dexmedetomidine. In second group the patients were given 1 mg/kg meperidine. In third group, no sedative were done but they were given 0.1-.02 mg fentanyl through intravenous. Here, the heart rate, hemoglobin oxygen structure and mean arterial pressure were observed as parameter.

In statistical analysis result were expressed as mean± standard value for continuous variables, number of occurrence, percentages.

Outcome: For the 1st group heart rate were below 50 beats/min and Map below 70%. For heart rate, 2nd and 3rd group showed 79±14 and 89±18 per minute respectively. MAP was for 2nd and 3rd group 101.4±16.7 and 103.4±17.9 mmHg respectively. This study's result showed that the heart rate and MAP rate was not much variable. It also showed the analgesic effect significantly.

In another article, to observe sedative effect by using DEX on pediatric burn patient was done. For this study 65 pediatric burn patient were selected as participant. In this case the patients were took the drug by infusion. The patient was monitored in the hospital continually. For observation, the data recorded were, patient age,weigth, burn size,dose and duration of infusion, and absence or presence of mechanical ventilation. Sedation were evaluated by nursing staff during the studied time period. The study was conducted for six months.Thoracic independence, pulse oximetry, CO_2 measurement and electrocardiogram also monitored for 24 hours. Blood glucose was monitored in 2times period within24 hours. (Walker et al., 2006)

Harmful effects of tepazepam in older adults , who are suffering from chronic insomnia.

The purpose of this study was to find out tepazepam's adverse effects in older adults who were suffering from chronic insomnia. (Morin et al., 2003)

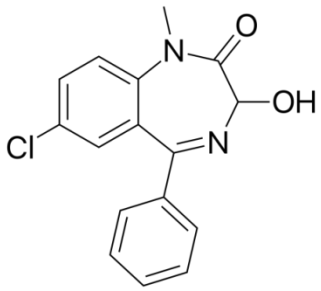

Figure 14: Tepazepam

Therapeutic effects: This drug is use to treat anxiety, insomnia.

Assay Method: This study basically had showed the cognitive - behavioral therapy (CBT) effects as combined and separately. Pharmacology treatment in older patient for late life insomnia. For this study, seventy eighth healthy participant wete selected who were 55 years or more than 55 years old. They were randomly given temazepam (20 patient), combination

of tepazepam and CBT (20 patient), drug placebo (20 patient) and only CBT (18 Patient). The participates were compared in every treatment regimen according to their gender, age, educational level marital status and insomnia duration. All patient were met the international classification of sleep disorder (ICSD) criteria for chronic insomnia and primary insomnia. The patient were reported that more than 30 min awake were spaded per night. The patient was excluding if they had major depression, severe cognitive impairment or other psychological evidence. For this study adverse effect questionnaires, data analysis, sleep diary, and some other measure were done. The patient was given the drug orally at night before 60 min of bed time by the instructed physician. The placebo and drug were identical in color and shape. The dose was given 7.5mg to 30 mg based on side effect and treatment response. The medication was given 2 to 3 times in a week for 8 weeks. The treatment was done by following the NIH guidelines. Moreover, the patient was evaluated in every week by psychiatrist.

Outcome: There was no significant difference in demographically among three groups. Among 60 participants only 54 participant were completed the treatment. Of the 54, 17 patient were taken temazepam, 18 were taken placebo and 19 were taken combination treatment In this treatment 2 temazepam patient and 1 combination patient were dropped out due to sever adverse effects. For temazepam, the average adverse effects per patient were 18.8, for placebo 25.6 and for combination 21. Over the treatment, 60% patient gave less than 20 complaint(11 for tepazepam, 12for combination and 9 for placebo). 15% patient gave complain between 20 to 30 adverse effects.25% patient were reported adverse effect more than 30. The most adverse effects intensity were, day time sedation (mean 0.5), headache (mean.0.36), diarrhea and impaired coordination (mean 0.16). The degree of compliance after end of study was, 4.7 out of 5 for temazepam received patient, 4.6 out of 5 for placebo received patient and 4.2 out of 5 for combination received patient.

In this article results is given below:

Table 4: Patient demographics and treatment Characteristics

Age (Yrs)	**5±5 (0.6-17)**
Sex (M+F)	42 (65%) : 23 (35%)
Weight (Kg)	26±20 (8-100)
Mechanical Ventilation (Y:N)	42 (65%) : 23 (35%)
% of burn	36±23 (3-94)
Loading Dose (Y:N)	26 (40%) : 39 (60%)
Treatment Length (days)	11±10 (2-50)
Average hourly dose (ug/kg/hr)	0.5±0.3 (0.1-2)

Table 5: Comparison of sedation rating before and after the initiation of dexmedetomidine

Sedation Rating	**Adequate**	**Inadequate**
Post-DEX	65	0
PRE-DEX	0	65

Chapter 3

3.1 Conclusion

From the above articles review, it can be said that, the use of common sedative hypnotic drug for example benzodiazepine drugs, z- drug(zolpidem, zopiclone etc) and others sedative hypnotic drug have more adverse effects. The common adverse effects were found central nervous system depression, drowsiness, somnolence, respiratory depression. In addition, these drugs have major adverse effect on older adults and pregnant women found by the articles reports. The long term use of these drug in older adults cause fracture (arms, hip and femur), pulmonary obstruction, and short term memory loss occurred commonly. The use of this drug during pregnancy has adverse effects on mother as well as the fetus as these drugs can cross placenta. During pregnancy, these drugs can cause miscarriage, early delivery, drug dependence, panic disorder, suicidal thought. Additionally, the fetus is affected by low birth weight, congenital malformation and other mental disorder. On the other hand, it also found that, the sedative hypnotic drugs have additional therapeutic effects. For example alprazolam has analgesic effect which helps to reduce pain. Additionally, it also found by the articles, there are some plant extracts and new molecule develop as sedative hypnotic drug, which have less adverse effect than sedative hypnotic drugs. These extract and new molecule also give some additional therapeutic effects other than sedative hypnotic effect. For example, indiplone is a new molecule developed as sedative hypnotic drug also showed antiagregation property with less adverse effect. This drug may help to the cardiac patient with anxiety disorder. The plant extract contain phenolic acid, alkaloids, flavanoids, which give sedative and hypnotic effect as well as other therapeutic effect. For example, ginsenosides showed anti inflammatory, anti diabetic and cancer chemo prevention effects with sedative hypnotic effects.

To avoid the adverse effects caused by sedative hypnotic drugs new drug molecules can be developed like Indiplone. The plant extract also can be developed as drug to avoid adverse effects. Because, these extract have same sedative hypnotic affect comparison to benzodiazepine an z drugs. On the other hand, to maintain anxiety disorder and healthy mental status a healthy diet should be maintained. For pregnant women regular physical exercise, yoga, meditation can help for preventing anxiety and good sleep. The adults also should maintain a healthy diet and not taking much caffine, also maintain the regular meal taking and sleep.

3.2 Future Plan

In future, this study will help to develop new molecule as sedative hypnotic drugs, which will have less adverse effects. Again, for another therapeutic purpose these drugs will be used. It will also help to safe use of sedative hypnotic drugs. New molecule synthesis can be done from the plant extract, which was showed sedative hypnotic effect and used for long time. Through this study we believe that fellow students and researchers will be benefited in the future to do future research.

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