Pharmacokinetic and Pharmacodynamics study on Antidepressant Activity of Dextromethorphan and Bupropion

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Abstract: The large percentage of adults with Major Depressive Disorder (MDD). In these article we study the antidepressant drug that is Dextromethorphan (DXM) and bupropion (BUP) In that study of mechanism of action of the dextromethorphan and bupropion drug. In that also include there brand name, trade name, other name, license data and study about inhibition metabolism of dextromethorphan (CYP2D6 Substrate) by the enzyme Bupropion (CYP2D6Inhibitor) bupropion distribution and metabolism, side effect, adverse reaction of dextromethorphan and bupropion
Keywords: Dextromethorphan, Bupropion, Major Depressive Disorder

I. Introduction:

A novel, oral, investigational NMDA (N-methyl-d-aspartate) receptor antagonist with multimodal activity is currently being developed for the treatment of central nervous system disorders. This agent combines the NMDA antagonist dextromethorphan with the norepinephrine–dopamine reuptake inhibitor bupropion [1] Nonopioid central antitussive that is dextromethorphan which is inhibited tractus solitaries

(TS)-evoked synchronous release of glutamate in the second-order NTS neurons independently of its agonistic effect on the sigma receptor Furthermore, DEX decreased spontaneous release of glutamate under blockade of the voltage-dependent Ca2+ channels, which are suggested to be possible targets of DEX However, there is still limited knowledge of its cellular mechanisms[2] metabolism of 25% of all clinically relevant drugs but also due to its highly polymorphic nature and how this variability significantly impacts drug metabolism within and among worldwide populations . Over 100 allelic variants have been defined to date by the Pharmacogene Variation Consortium[3]The neural basis of apathy in dopamine transporter (DAT)has been examined in several neuroimaging studies. From a neurotransmitter perspective, low levels of dopamine are associated with reduced motivational and reward-driven behavior and have been linked to apathy. [4]Bupropion (synonym: amfebutamone; (± or rac)- 2-(tert-butylamino)-3'chloropropiophenone;1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino)]-propan-1-one; 2-(tert-butylamino)-1-(3-chlorophenyl)propan-1-one) was first described in 1969 (Mehta 1969) and then approved in 1985 by US Food and Drug Administration (FDA) as a major depressive disorder treatment, with a maximum dose of 900 mg/d. Due to high incidence of seizures in bulimic patients, bupropion was subsequently withdrawn from the market.[5] Bupropion is believed to exacerbate anxiety and should not be prescribed in anxious depression. This is a myth. Truth is that in a meta-analysis,5 with pooled individual patient data from 10 randomized, double-blind, placebo-controlled trials, to compare the efficacy of bupropion to SSRIs in treating anxious depression. No difference in timing or degree of improvement in anxiety symptoms between groups based on Hamilton Anxiety Scale or Hamilton Depression Rating Scale—Anxiety-Somatization (HDRS-AS) scores, was found. Moreover, in a pilot-controlled trial of bupropion XL vs escitalopram in GAD, bupropion demonstrated comparable anxiolytic efficacy to escitalopram and was well tolerated([6])Major depressive disorder (MDD) is one of the leading causes of disease disability worldwide with approximately 260 million individuals globally affected MDD is associated with a reduced quality of life as well as significant occupational and economic costs as a consequence of pervasive and enduring psychosocial and role impairment (i.e. social economics) . The enormous disease burden of MDD invites the urgent need for innovative, safe, and effective disease-modifying treatment [7]. A single-crystal structure of the ethanol hemisolvate of racemic bupropion HCl exists in the literature [18]. However, due to an apparent difficulty in preparing a single crystal of adequate size and quality, the reported crystal structure for desolvated racemic bupropion HCl is based on a powdered crystalline sample, not a single-crystal sample[8] Bupropion is an atypical antidepressant that is structurally similar to amphetamines. Its primary toxic effects include seizure, sinus tachycardia, hypertension, and agitation; however, at higher amounts of ingestion, paradoxical cardiac effects are seen[9] Bupropion SR inhibits neuronal reuptake of dopamine and norepinephrine in the reward center of the brain, which may stimulate rewards similar to those achieved when smoking, thus reducing the craving for nicotine [10]

II. Methodology:

Exclusive information is taken from pub-med, science hub. in these article we study Pharmacokinetics and Pharmacodynamics of action of dextromethorphan and bupropion with diagrammatically mechanism of action also study

of side effect of the dextromethorphan And Bupropion, Adverse drug reaction in that also included chemical structure of the dextromethorphan and Bupropion and there estimation method

III. Chemistry of Dextromethorphan and Bupropion

Dextromethorphan, like ketamine and phencyclidine, is one of a class of compounds known as dissociative agents Despite its abuse potential, however, dextromethorphan was never classified as a controlled substance. Dextromethorphan is a more complex molecule than its congeners but it nonetheless contains an alkylated amine adjacent to a cyclohexane ring, a structural moiety common to the dissociative agents. Dextromethorphan is the dextrorotatory stereoisomer of the left-handed codeine analogue levorphanol. It has a bridged phenanthrene nucleus, a structural motif found in morphine analogs, but its opposite handed stereochemistry limits binding into mu and delta opiate receptor

Structure of Bupropion

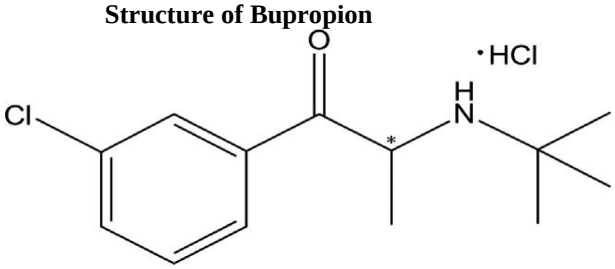


Figure No. 1 Bupropion

Systematic Chemical Name 1-(3-Chlorophenyl)-2-[(1,1-dimethylethyl) amino]-1-propanone;
Synonym: -2-(tert-butylamino)-30 -chloropropiophenone
Nonproprietary Names: Bupropion, Amfebutamone Proprietary names, Wellbutrin, Zyban, Voxra, Budeprion, Prexaton, Elontril, or Applenzin
Molecular formula: C13H18ClNO.HCL
Molecular weight: 276.20
CAS Number: 31677-93-7

Dextromethorphan

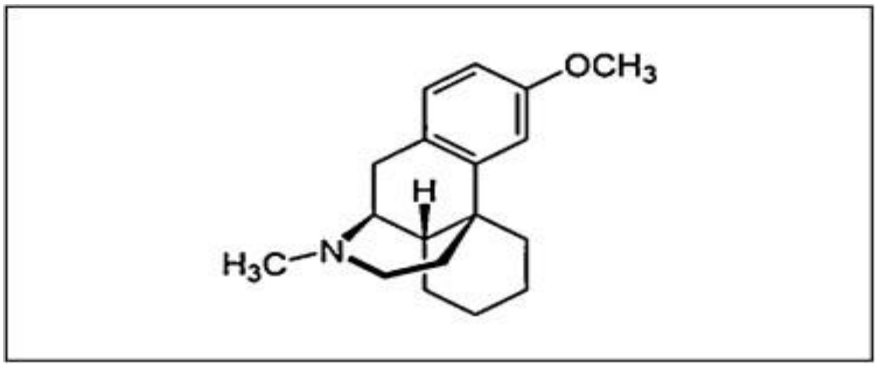


Figure No. 2 dextromethorphan
Chemical formula: C18H25NO
Molecular formula: 271.4 g/mol
Chemical name: **(+)-3-methoxy-17-methyl-9*α*,13*α*,14*α*-morphine**.
Dextromethorphan is the dextrorotatory enantiomer of levomethorphan, which is the methyl ether of levorphanol, both opioid analgesic

IV. Absorption

Dextromethorphan

DXM is Mostly administered the typical dose as antitussive being in patients over 12-years-old, 10–30 mg taken three to six times per day or extended release formulations 60 mg twice per day, in a Maximum dose of 120 mg [11]. First patented in 1949, DXM is a non-opioid antitussive agent that has been implemented in over-the-counter cough syrup and cold medications [12] Exposure to dextromethorphan is increased &20-fold following single or repeated administration of dextromethorphan/quinidine 30/10 mg versus dextromethorphan alone]. Maximum plasma concentrations (C -max) of dextromethorphan and quinidine are attained &3–4 and &2 h, respectively, after repeated administration of dextromethorphan/quinidine 20/10 or 30/10 mg [13]
In healthy volunteers who were extensive metabolizers and who received dextromethorphan/ quinidine 30 mg/10 mg twice daily for 7 days, a maximum mean plasma concentration (C-max) of dextromethorphan of 63.7 ng/mL was reached after a mean of 3.71 hours, with a mean area under the plasma concentration-time curve Area under cure from time 0 to 8 hours (AUC8) of 451.7 ng h/mL [14] B. The role of DXM in the treatment of neuropathic pain is still uncertain. As an N-Methyl-D-aspartate receptor

antagonist, it has the potential to play a role in pain blockade. However, its analgesic effectiveness on a general scale remains unclear. The dose needed to produce sufficient analgesia also remains undefined. The numberof current studies is limited, are conducted in small populations, and have reported contradicting results [15]

V. Bupropion

Bupropion is administered per os; the absorption is fast (T-max 1.3–1.9 h) for immediate release formulation and not influenced by the presence of food [16] bupropion 2 In humans, absolute oral bioavailability is unknown since an intravenous formulation is currently not available. Nevertheless, similar relative bioavailability results were found for immediate release and sustained release formulations, as evidence by the Area under curve, and in comparison, a bioavailability of 68% was observed for extended release formulations, probably due to less absorption or increased metabolism [6] A two-phase trial evaluated the long-term efficacy and weight change of fixed dose (300 mg/day) bupropion[17]. Administered bupropion dosed at 150-300mg/day in an open-label design for 8 weeks (phase I) [7]

Bupropion is given with combination of dextromethorphan centrally-acting mechanisms of action, is a compelling choice as metabolic inhibitor of dextromethorphan and suggests the potential for pharmacological synergy and clinical use across a broad range of neuropsychiatric conditions. Dextromethorphan/bupropion is currently in late- stage clinical development for major depressive disorder (including treatment-resistant depression), Alzheimer's disease agitation, and smoking cessation[18]

VI. Bioavailability of dextromethorphan And Bupropion

A strategy for boosting the efficacy of a drug by inhibiting the cytochrome oxidase system has only been recently considered, and the chronological development of this concept with regard to DXM is reviewed here. There are a number of scenarios that make this an attractive approach, particularly for DXM in which the parent compound and principal metabolite Dextrorphan exhibit different receptor-binding properties. DXM and dextrorphan both act as non-competitive NMDA antagonists and have affinity for sigma-receptors [19] Plasma and urine samples dextromethorphan were analyzed using liquid chromatography-mass spectrometry and the resulting data analyzed using non-compartmental analysis. The C-max T-max and the t1/2 of dextromethorphan were 519.4 ng/mL 0.55 h and 12.4 h respectively. The area under the curve of dextromethorphan free dextrorphan and conjugated dextrorphan were 563.8, 2.19, and 6,691 hng/mL respectively [20] bupropion therapeutic dose is 150-300 mg/ day bupropion target enzyme CYP2B6. The mean plasma drug concentration of bupropion is 8 ng/mL when 2 hour sampling[21

VII. Mechanism of action dextromethorphan.

DXM may exert its neuroprotective effects to inhibit glutamate neurotoxicity through multiple actions. Abnormally elevated concentrations of glutamate lead to toxic increases in cytosolic free calcium culminating in neuronal necrosis or apoptosis. DXM can reduce presynaptic calcium dependent glutamate release [22] Dextromethorphan Current bias is that DXM is principally acting as a -1 receptor agonist [23]. s Receptors modulate are neurotransmitter release and DXM has been show to decrease the concentration vitro .DXM is also block the voltage –activated Na and Ca channels .being the last involved in local anesthetic effect .DXM block the motor function by static nerve at dose-dependent local anesthetic effect of DXM [24] , the portfolio of receptors recruited by dextromethorphan and the degree of occupancy of each receptor by this agent depend upon the concentration of dextromethorphan in the brain, which at therapeutic doses for PBA would be predicted to occupy substantial numbers of the receptors for which dextromethorphan has lower affinity and to saturate the receptors for which dextromethorphan has higher affinity. Which receptor or combination of receptors mediate(s) the therapeutic action of dextromethorphan in PBA is unknown, but some theories suggest it might be a combination of the serotonin transporter (some antidepressants improve PBA), the sigma 1 receptor, and the NMDA receptor (since dextromethorphan/quinidine appears to have more robust and sustained effects in PBA than antidepressants [25] Dextromethorphan is a noncompetitive N-methyl-D-aspartate receptor antagonist that has been reported as a potential treatment modality at antitussive doses of 1-2 mg/kg (maximum 60 mg/dose) by mouth twice daily; however, dextromethorphan use is limited in patients unable to take enteral medications.[26]

VIII. Signaling Pathway Targeted by

DXM Both nuclear factor-kappa-B (NF-κB) and activator protein-1 (AP-1)-signaling pathways, which are two major factors in inflammatory responses, are involved in TNF-α-induced MMP-13 expression the molecular mechanisms underlying the anti-inflammatory effects of DXM were examined. DXM inhibited TNF-α-induced NF-κB DNA binding activity. In support of those results, the TNF-α-stimulated nuclear levels of both p65 and p50 decreased after DXM treatment , DXM counteracted TNF-α-mediated IκBα degradation and retained higher levels of IκBα in the cytosol The mechanism is likely to involve the down regulation of TNF-α-induced IκBα kinases, IKKα/β, by DXM. In addition to the NF-κB signaling pathway, DXM inhibited TNF-α-induced AP-1 DNA binding activity. The investigation into the upstream kinases mitogen-activated protein kinases (MAPKs) that regulate AP-1 activation revealed that DXM selectively inhibited TNF-α-induced expression of phosphorylated JNK and c-Jun (an indicator of c-Jun N-terminal kinase activity), and had no effect on expression of phosphorylated extracellular-p38 [27]

IX. Mechanism of action bupropion

Bupropion, originally developed as an antidepressant, inhibits dopamine and noradrenaline reuptake [28] Combination therapy with naltrexone, an opioid antagonist, and bupropion, a norepinephrine and dopamine reuptake inhibitor [29]

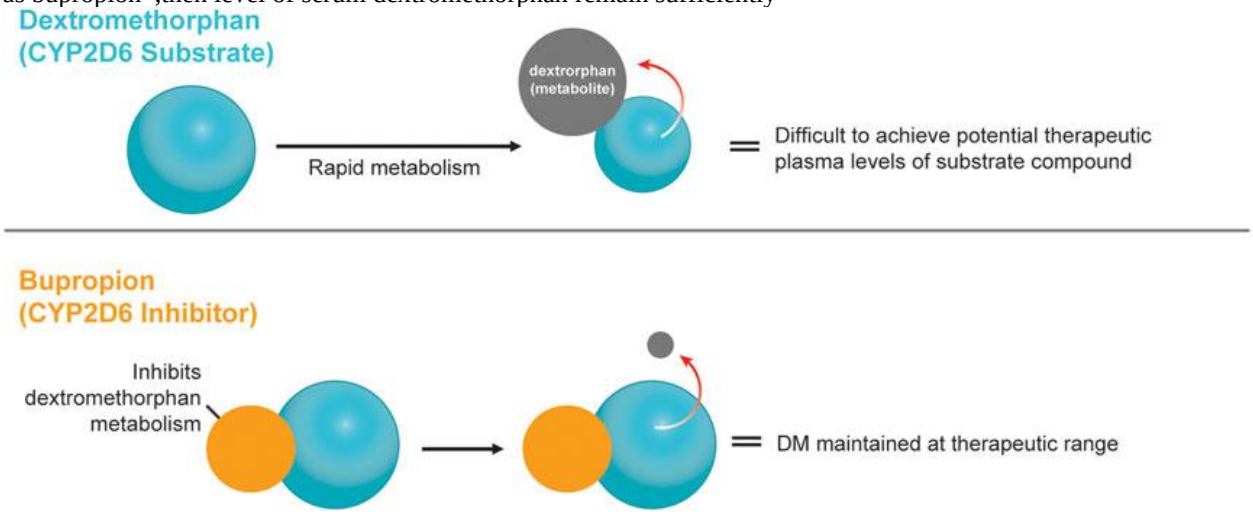
selective serotonin reuptake inhibitors(SSRI) mechanism of the SSRI it increase the risk is the attenuated coagulative function of serotonin from platelets . Generally platelet activity due to the platelet –released serotonin . serotonin receptor is present on surface

on the surface of the platelet .due to SSRI inhibit serotonin reuptake and decrease the availability of serotonin the platelet which reduce the coagulative effects of serotonin [30] Mechanism of action of bupropion involve in reuptake inhibition of the catecholamine's dopamine and noradrenaline, a profile similar to the presumed action of psych stimulants. The powerful influences that catecholamine's have on the brain circuits that appear to be altered in Attention Deficit Hyperactivity Disorder [ADHD] are mediated through stimulation of dopamine 1(D1) and noradrenergic 2a receptors, respectively [31]

Bupropion effects on cardiopulmonary coupling variables The CPC bupropion effects observed in this study compliment the standard PSG measures. The CPC results suggest that bupropion effects are not limited to central nervous system but also impact peripheral systems demonstrating an inter-linked physiological process that includes autonomic cardiac, respiratory and electro cortical systems. VLFC showed a statistical trend to be increased with bupropion and a negative association to sleep efficiency. Unmediated depressed patients receiving hypnotics showed no difference in stable sleep, unstable sleep and VLFC compared to controls suggesting hypnotic use decreases VLFC and LFC and increases HFC. VLFC associates with REM and wake REM sleep has the lowest cardiorespiratory phase synchronization indicating elevated cardiovascular risk . reported the highest occurrence of adverse cardiac events is found in REM sleep[32]

X. Mechanism of action of dextromethorphan and bupropion

Dextromethorphan and bupropion is approved by food and drug administration for humans as antidepressant when dextromethorphan is given alone then it is rapidly metabolized by the hepatic enzyme CYP2D6 into dextrophan.after metabolism process of dextromethorphan level in serum is minimal .However if dextromethorphan is administer with CYP2D6 inhibitor such as bupropion ,then level of serum dextromethorphan remain sufficiently [33]



Systematically representation of inhibition of dextromethorphan metabolism by bupropion (CYP2D6 Inhibitor)

when dextromethorphan and bupropion is given in combination form then mechanism of action of antidepressant therapeutic classes into one therapeutic agent both are dextromethorphan and bupropion increases norepinephrine availability by inhibiting reuptake and acting as alpha- 4-beta-2 nicotinic (nACh) antagonists. In addition, bupropion increases dopamine availability by blocking reuptake, while dextromethorphan increases glutamate by acting as an NMDA receptor antagonist and serotonin .by both acting as a serotonin reuptake inhibitor and boosting serotonin activity in the dorsal raphe via sigma-1 agonism[34]

XI. Adverse event reporting system analysis

DXM over the first 3 years of CHPA's abuse mitigation plan, CHPA commissioned a search of the FAERS database (2010–2013) using terms related to abuse.[35] Significant antagonism of the NMDA receptor causes analgesia, amnesia, hallucinations, delusions, agitation, mood dysregulation, and dissociative anesthesia[36] These include induction of an out-of-the body dreamy state, disorientation, depersonalization, confusion, somnolence or stupor, impaired coordination, agitation, distortions of motion or speech, and dissociative anesthesia. Visual hallucinations are common after the taking of high doses (>2.5 mg.kg). Experimental evidence in rat models suggests that the mental effects of DXM are in large measure caused by the active metabolite dextrorphan, which binds to the same CNS receptor asphencyclidine.[37] From the standpoint of pediatric neurology, we are in fact very interested in the field of NMDA blockade with regard to the treatment of severe epilepsy or to neuroprotection. [38] In order to assess whether the policy changes meant to limit access to DXM were impactful, the DXM problem in Okinawa was reassessed a year after these Dextromethorphan (DXM) is used in numerous cough and cold medications for its anti-tussive effects. It can cause agitation, ataxia, hypertonic, sedation and may produce dissociative hallucinations at high does[39] changes took effect. First, we compared sales records to assess if sales of DXM containing medications were decreasing [40] ccasionally, drowsiness, dizziness, nausea and abdominal discomfort, flatulence, diarrhea or constipation are observed .constipation, a frequent opioid side-effect, is much less pronounced since DXM has no relevant activity on m-opioid receptor and r1R[41]

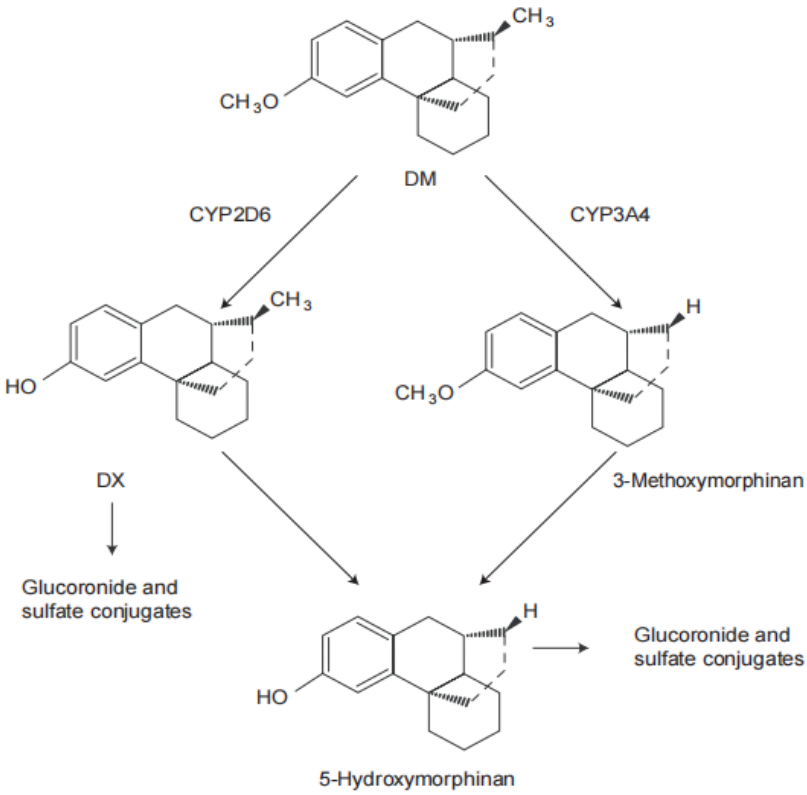


Figure No. 3 DXM Metabolism

DMX structure and metabolism :DXM is a dextroratory enatomer of levorphanol. DM is extensively metabolised in > 90% of the population by the hepatic CYP2D6 enzyme, which catalyses the Odemethylation of DXM to its main metabolite Dextrorphan DX An alternate pathway is mediated primarily by CYP3A4 and N-demethylation to form 3-methoxymorphinan. Information from DXM: Dextromethorphan; DX: Dextrorphan [23] Dextromethorphan, together with its major metabolite dextrorphan, exhibits NMDA antagonist characteristics and also possesses multiple mechanisms of action such as a nonselective serotonin reuptake inhibitor, a R-1 receptor agonist, and a voltage-gated calcium channel antagonist. In a recent article by Lauterbach, the author has proposed that dextromethorphan and its metabolite dextrorphan may have a beneficial effect on treatment-refractory depression based on their pharmacodynamic similarities to ketamine including R-1 agonist and NMDA antagonist properties, calcium channel blockade, muscarinic binding, serotonin transporter inhibition, and K-receptor potentiation. Dextromethorphan's limited clinical benefit to the central nervous system is proposed to be associated with its rapid metabolism to dextrorphan, which restricts its central bioavailability and therapeutic utility. Systemic concentrations of dextromethorphan can be increased via coadministration of low-dose quinidine, which reversibly inhibits its first-pass elimination.A combination of dextromethorphan 20 mg and quinidine 10 mg twice daily has been proven to treat pseudobulbar affect in United States[42]

XII. Metabolic interactions dextromethorphan

Besides grapefruit juice, several other metabolic interactions have been described. Curcuma longa is used as a traditional medicine and can significantly inhibit human CYP2D6 and CYP3A4 activities. As a result, it was shown that Curcuma longa extracts inhibited the enzyme CYP2D6 and CYP3A4 mediated O- and N-demethylation of DXM into DXO and 3methoxymorphinan, respectively, in a dose-dependent and linear fashion [43]

XIII. Metabolism of bupropion

Presents the metabolic pathway of bupropion. Various studies suggest that both bupropion enantiomers undergo extensive, stereo selective and interindividual differences of the phase I and II hepatic metabolism by (i) hydroxylation of the tert-butyl moiety to an unisolated hydroxybupropion, followed by ring closure, to the phenylmorpholinol metabolite (also sometimes referred to as hydroxybupropion); (ii) aromatic hydroxylation at 4'position to produce 4'-hydroxy-bupropion; (iii) reduction of the ketone group by 11b-hydroxysteroid dehydrogenase-1 (11b-HSD-1) and aldoketoreductase to the diastereoisomers erythro and threo amino alcohols, threohydrobupropion and erythrohydrobupropion, followed by further aromatic hydroxylation at 4'position to produce threo/eythro-4'-hydroxy-hydrobupropion or aliphatic hydroxylation; (iv) side-chain cleavage to m-chlorobenzoic acid, followed by glycine conjugation to m-chlorohippuric acid; (v) hydration of bupropion; (vi) aliphatic and aromatic hydroxylation of threo/erythrohydrobupropion; and (vii) glucuronide or sulfate conjugation of phase I metabolites. [44] The pharmacological and toxicological effects of bupropion are attributed bupropion and t also to its three active metabolites such as hydroxybupropion, (50% as potent), threohydrobupropion and erythrohydrobupropion, (both 20% as potent), which circulate at higher plasmatic concentrations comparatively to bupropion[45]Bupropion is a nonnicotine treatment for smoking cessation.In humans, bupropion is

metabolized by the genetically polymorphic enzyme CYP2B6 to hydroxybupropion. Hydroxybupropion may contribute to bupropion's pharmacologic activity. Pharmacodynamically, hydroxybupropion demonstrates similar or greater inhibition effects (half-maximal inhibitory concentration) as compared with bupropion in blocking dopamine, norepinephrine transporters, and the α4β2 nicotinic receptor in vitro; in addition, it blocks the development of nicotine-induced condition place preference and reduces the somatic signs of withdrawal in animal models.9,10 Pharmacokinetically, hydroxybupropion has a 10 times higher free-plasma concentration at steady state and a slightly higher unbound fraction as compared with bupropion, resulting in considerably higher hydroxybupropion drug exposure than bupropion exposure at steady state.Together, these properties suggest that hydroxybupropion may play an important role in mediating the smoking-cessation effects of bupropion[46] 1 Bupropion and its primary metabolite, hydroxybupropion, decrease the reuptake of DA and NE via synaptosomes. Also, bupropion, given acutely, increases the synaptic level of DA and NE, which then inhibits neuronal firing via negative feedback.Bupropion HCl has shown to have noncompetitive nicotinic antagonistic effects, which is thought to contribute to its antidepressant effects, as well as to its effectiveness as a smoking cessation drug. There are formulations of bupropion HCl: immediate release taken thrice daily with peak plasma concentration in 2 hours, sustained release (SR) taken twice daily (BID) with peak plasma concentration in 3 hours, and extended release (XL) taken once daily with peak plasma concentration in 5 hours[47]

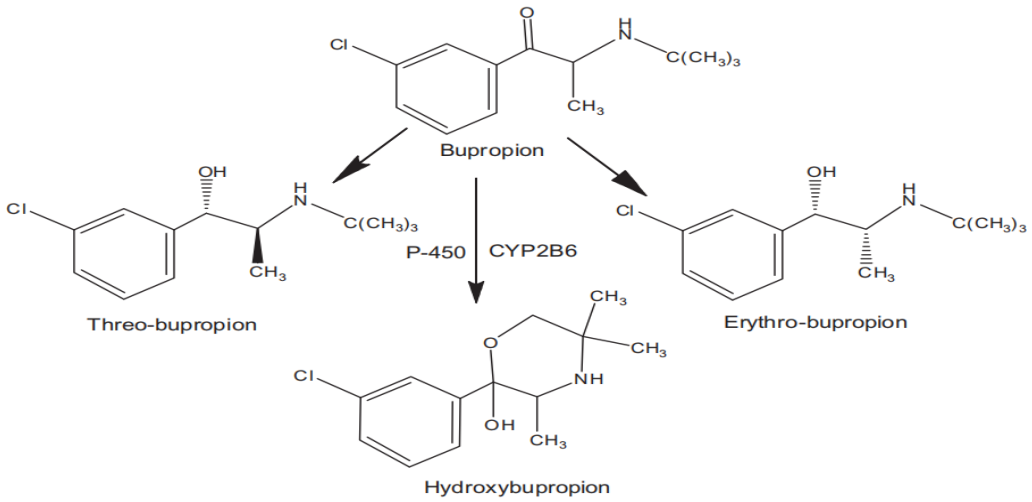


Figure No.4

XIV. Bupropion Metabolism

Metabolic interactions of bupropion

Bupropion is a strong in vivo CYP2D6 inhibitor, increasing the concentration of CYP2D6-metabolized drugs, such as desipramine, atomoxetine , and nebivolol

However, in vitro studies suggested that bupropion and hydroxybupropion were weak CYP2D6 inhibitors , while threohydrobupropion and erythrohydrobupropion were relatively stronger CYD2D6 inhibitors[48] BUP is primarily metabolized in the liver by cytochrome P450 enzymes, 11β-hydroxysteroid Dehydrogenase-1 (11β-HSD1), and aldoketoreductases The three resulting metabolites, Hydroxybupropion (OHB), Erythrohydrobupropion (EB) and Threohydrobupropion (TB), are also pharmacologically active, with OHB being 50- 100% and TB and EB being 20% active as BUP OHB and TB, but not EB, circulate at 3 – 30-fold higher concentrations than the parent drug[49]

Three cohort studies reported foetal loss following bupropion exposurewith only one study including control group The GlaxoSmithKline "Bupropion Pregnancy Registry" cohort reported data from 994 prospectivelyregistered pregnant women (featuring 1005 monitored foetuses) following gestational bupropion exposure. Following first trimester bupropion exposure there were 669 live births, three foetal deaths occurring at or later than 20 weeks gestation, 38 induced abortions, and 96 spontaneous pregnancy losses occurring before 20 weeks. Following second trimester exposure there were 145 live births, one induced abortion and one spontaneous pregnancy loss and after bupropion exposure in the third trimester there were 51 live births and one foetal death. 603 prospectively-registered pregnancies were either lost to follow-up or pending delivery when the register closed, resulting in a loss of outcome data.[50]

XV. Elimination

The half-life of bupropion is 3-4 hour Human studies using radiolabeled bupropion showed that bupropion and its metabolites are excreted in urine (88%) and in the feces (10%); less than 1% of bupropion is excreted unchanged in the urine and occurs mainly as threohydrobupropion [51]

Table No. 1

Dextromethorphan	NMDA receptor sigma1 receptor agonist serotonin-norepinephrine reuptake inhibitor, nicotinic acetylcholine receptor negative allosteric modulator and other action
Bupropion	Norepinephrine- dopamine reuptake inhibitor and nicotinic acetylcholine receptor antagonist
Trade name	Auvelity
Other name	DXM/ BUP,AXS-05
License dada	US daily med; Dextromethorphan and Bupropion (https;//dailymed.nlm. gon/ dailymed/ search cfm Labeltype=query= Dextromethorphan +an+bupropion
Routes of Administration	By mouth

XVI. Clinical studies on DXM antidepressant effects

The antidepressant effects observed were sustained for up to 20 days with daily administration, with a gradual loss over the ensuing 7 days and eventually full MDD relapse . In a separate case report, researchers found that in a 32-year-old female patient with TRD, affective lability, and borderline personality disorder, the combination of DXM/Q at 20 mg/10 mg daily for 1 year improved the patient's mood lability, crying spells, and affective control, as demonstrated by
Reductions in the Center for Neurologic Study-Lability Scale (CNS-LS) scores[52]

XVII. Discussion;

In the review paper we discuss about the separately and combination study of the both drug that is dextromethorphan and bupropion .in study of mechanism of action of separately dextromethorphan and bupropion and study of combination effect of both drug. Generally dextromethorphan is use as anti-tussive, whereas bupropion is use in various diseases condition like Alzheimer disease anti -depressant , the recently approved formulation that is Auvelity. Which contain dextromethorphan hydrobromide 45 mg and bupropion is 105 mg .In these article also discuss about dose rough of administration of drug ,side effect ,study of the metabolism of these drug means how to metabolism in vivo .

References

1. Stephen M. Stahl, Dextromethorphan/Bupropion: A Novel Oral NMDA (N-methyl-d-aspartate) Receptor Antagonist with Multimodal Activity ,(2019)

2. Yoshiaki Ohi Daisuke Kodama Akira Haji, Involvement of the cAMP-Dependent Pathway in Dextromethorphan-Induced Inhibition of Spontaneous Glutamate Transmission in the Nucleus Tractus Solitarius Neurons of Guinea Pigs,(2018),
3. Evelyn Marie Gutierrez Rico a , Aoi Kikuchi a , Takahiro Saito a , Masaki Kumondai a, CYP2D6 genotyping analysis and functional characterization of novel allelic variants in a Ni-Vanuatu and Kenyan population by assessing dextromethorphan O-demethylation activity, CYP2D6 genotyping analysis and functional characterization of novel allelic variants in a Ni-Vanuatu and Kenyan population by assessing dextromethorphan O-demethylation activity

4. Franziska Maier, PhD; Annika Spottke, MD; Jan-Philipp Bach, MD; Claudia Bartels, PhD; Katharina Buerge, Bupropion for the Treatment of Apathy in Alzheimer Disease A Randomized Clinical Tria(2020) ,1/14

5. Rafaela Costaa , Nuno G. Oliveirab and Ricardo Jorge Dinis-Oliveiraa, Pharmacokinetic and pharmacodynamic of bupropion: integrative overview of relevant clinical and forensic aspects,(2019)

6. Ahmed Naguy1 and Bassem H.M. Bad, Bupropion—myth-busting!(2021)

7. Amna Majeed, Jiaqi Xiong, Kayla, M. Teopiz, Jason Ng, Roger Ho, Joshua D. Rosenblat, Lee Phan, Bing Cao & Roger S. McIntyre, Efficacy of dextromethorphan for the treatment of depression: a systematic review of preclinical and clinical trials,(2021)

8. S.R. Khan, R.T. Berendt*, C.D. Ellison*, A.B. Ciavarella*, E. Asafu-Adjaye*, M.A. Khan† , P.J. Faustino, Bupropion Hydrochloride,(2016)
9. YUANJIA ZHU TIWALOLA KOLAWOLE, MD XAVIER F. JIMENEZ, MD, YUANJIA ZHU TIWALOLA KOLAWOLE, MD XAVIER F. JIMENEZ, MD,(2016), . 22, (5): 405
10. Tiffany Vogeler, PharmDa , Claire McClain, PharmDb , and Kirk E. Evoy, PharmD, BCACP, TTS, Combination bupropion SR and varenicline for smoking cessation: a systematic review,(2016).
11. Ana Rita Silva & Ricardo Jorge Dinis-Oliveira, Pharmacokinetics and pharmacodynamics of d extromethorphan: clinical and forensic aspect, Drug Metabolism Reviews, (2020)
12. Amna Majeed, Jiaqi Xiong, Kayla M. Teopiz, Efficacy of dextromethorphan for the treatment of depression: a systematic review of preclinical and clinical trials Expert Opinion on Emerging Drugs,(2021), . 26, : 1, 63–7
13. Lily P. H. Yang • Emma D. Deek ,Dextromethorphan/cQuinidine: A Review of Its Use in Adults with Pseudobulbar Affect ,(2014)
14. .Edna Patatanian, Jessica Casselman,Dextromethorphan/Quinidine In Pseudobulbar Affect, (2014) 29,: (4)
15. Tonya M Criner and Carla S, Perdun Dextromethorphan and Diabetic,(1999),33:11
16. Rafaela Costaa , Nuno G. Oliveirab and Ricardo Jorge Dinis-Oliveira,Pharmacokinetic and pharmacodynamic of bupropion: integrative overview of relevant clinical and forensic aspects , Drug Metabolism Reviews,(2019)
17. Krisna Patel, Sophie Allen, Mariam N. Haque ,Bupropion: a systematic review and meta-analysis of effectiveness as an antidepressant,(2016),
18. Stephen M. Stahl Dextromethorphan/Bupropion: A Novel Oral NMDA (N-methyl-d-aspartate) Receptor Antagonist with Multimodal Activity , BRAINSTORMS—Clinical Neuroscience Update, s (2019), 24, 461–466
19. Richard Alan Smith, Dextromethorphan/quinidine: a novel dextromethorphan product for the treatment of emotional lability expert opinion on Pharmacotherapy, (2006),7:(18):2581-2598
20. Carley R Coradoa , Daniel.S, McKemiea , Heather K., Knycha,bPharmacokinetics of Dextromethorphan and its Metabolites in Horses Following a Single Oral Administration,(2016),9,(6):880-887
21. Victoria Rollason1, Médéric Mouterde2,Youssef Daali1,Safety of the Geneva Cocktail, a Cytochrome P450 and P-Glycoprotein Phenotyping Cocktail, in Healthy Volunteers from Three Diferent Geographic Origins,(2020)
22. *Linda L. Werling, PhD,*† Edward C. Lauterbach, MD,‡ and Ursula Calef, PhD ,*
23. Dextromethorphan as a Potential Neuroprotective Agent With Unique Mechanisms of tion The Neurologist ,(2007);13: 272–293
24. Richard Alan Smith, Dextromethorphan/quinidine: a novel dextromethorphan product for the treatment of emotional lability expert opinion on Pharmacotherapy, (2006),7:(18):2581-2598
25. Ana Rita Silva & Ricardo Jorge Dinis-Oliveira, Pharmacokinetics and pharmacodynamics of dextromethorphan: clinical and forensic aspect, Drug Metabolism Reviews ,(2020)
26. Stephen M. Stah, Mechanism of action of dextromethorphan/quinidine: comparison with ketamine(2013) , 18 (05) , pp 225 – 227
27. Mara Faye Rubin1 Alexis K. Kuhn, Management of methotrexate-induced neurotoxicity with aminophylline plus dextromethorphan in a pediatric patient with pineoblastoma,(2020),
28. Liv Weichien Chen 1,2 ID , Feng-Cheng Liu 3 , Li-Feng Hung 2, Chondroprotective Effects and Mechanisms of Dextromethorphan: Repurposing Antitussive Medication for Osteoarthritis Treatment.(2018),
29. Naltrexone/bupropion (Mysimba - Orexigen Therapeutics Ireland Limited) is a fixed-dose combination product for the treatment of adults who are obese or overweight with at least one weight-related comorbidity, as an adjunct to diet ,Naltrexone/bupropion for obesity,(2017),55 :11
30. Andrei C. Sposito1,2,Isabella Bonilha1,Beatriz Luchiari , Cardiovascular safety of naltrexone and bupropion therapy: Systematic review and meta-analyses,(2021),1-9
31. Kyoung-Sae Na, Han-Yong Jung, Seong-Jin Cho, Seo-Eun Cho, Can we recommend mirtazapine and bupropion for patients at risk for bleeding,(2018)
32. Wim Verbeeck1 , Geertruida E Bekkering2 , Wim Van den Noortgate3Bupropion for Attention Defificit Hyperactivity Disorder (ADHD) in adults, 12, 2011.
33. Preetam J. Schramma,n , Russell E. Polandb , Uma Rao, Bupropion response on sleep quality in patients with depression: Implications for increased cardiovascular disease risk,(2013)
34. Graham Blaira , Corinne Wellsa , Ashley Koa Dextromethorphan and bupropion reduces high level remifentanil self administration in rats, Pharmacology, Biochemistry and Behavior,(2020),
35. Stephen M. Stahl ,Dextromethorphan/Bupropion: A Novel Oral NMDA (N-methyl-d-aspartate) Receptor Antagonist with Multimodal Activity, BRAINSTORMS—Clinical Neuroscience Update, (2019), 24:461–466
36. David C. Spangler1 , Catherine M. Loyd, Dextromethorphan: a case study on addressing abuse of a safe and effective drug, (2016), 11:22
37. Laura B. Bernstein, PsyD, David Albert, MD, Carlos Baguer Long-term Dextromethorphan Use and Acute Intoxication Results in an Episode of Mania and Autoenucleation ,(2019), 00: 00,
38. Richard H. Schwartz MD ,Adolescent Abuse of Dextromethorphan , Clinical Pediatrics,(2005)

39. MD Akif Turna, MD Istanbul, Turkey ,Dextromethorphan in Pregnancy,(2001)*Cody Armstrong, USN, MC*; Michelle R. Kapolowicz, PhD*, Interventional Study of Dextromethorphan Abuse Within the U.S. Military Community in Okinawa, Japan. 2020,00:1-2
40. Justin L. Poklisa, *, Haley A. Mulderb , Michelle R. Peaceb, The unexpected identification of the cannabimimetic, 5F-ADB, and dextromethorphan in commercially available cannabidiol e-liquids[2018] ,
41. *Cody Armstrong, USN, MC*; Michelle R. Kapolowicz, PhD*,
42. Interventional Study of Dextromethorphan Abuse Within the U.S. Military Community in Okinawa, Japan. 2020,00:1-2
43. Ana Rita Silva & Ricardo Jorge Dinis-Oliveira, Pharmacokinetics and pharmacodynamics of dextromethorphan: clinical and forensic aspect, Drug Metabolism Reviews ,(2020)
44. Shih-Ku Lin, MD,Þ Chun-Hung Pan, MD, MS,* and Chia-Hui Chen, MDþ, A Double-Blind, Placebo-Controlled Trial of Dextromethorphan Combined With Clonidine in the Treatment of Heroin Withdrawal, (2014) 34,:(4), pp 5008
45. Ana Rita Silva & Ricardo Jorge Dinis-Oliveira, Pharmacokinetics and pharmacodynamics of dextromethorphan: clinical and forensic aspect, Drug Metabolism Reviews ,(2020)
46. Rafaela Costaa , Nuno G. Oliveirab and Ricardo Jorge Dinis-Oliveiraa,c,d, Pharmacokinetic and pharmacodynamic of bupropion: integrative overviewof relevant clinical and forensic aspects ,(2019)
47. Rafaela Costaa , Nuno G. Oliveirab and Ricardo Jorge Dinis-Oliveiraa,c,d, Pharmacokinetic and pharmacodynamic of bupropion: integrative overview of relevant clinical and forensic aspect(2019)
48. AZX Zhu, LS Cox,N Nollen, B Faseru, KS Okuyemi,JS Ahluwalia, CYP2B6 and Bupropion's Smoking-Cessation Pharmacology: The Role of Hydroxybupropion, (2012), 92:(6).
49. Theresa A. Schwitalla, MD,Raj A. Patel, MD,† Glenn Catalano, MD, Bupropion Hydrochloride Sustained Release and Diurnal Enuresis: A Previously Unreported Adverse Effect, (2019), 4:(6), pp 211
50. Rafaela Costaa , Nuno G. Oliveirab and Ricardo Jorge Dinis-Oliveiraa,c,d, Pharmacokinetic and pharmacodynamic of bupropion: integrative overview of relevant clinical and forensic aspect(2019)
51. Lyrialle W. Han, Chunying Gao, Yuchen Zhang, Joanne Wang, and Qingcheng Mao, Transport of Bupropion and its Metabolites by the Model CHO and HEK293 Cell Lines,(2018),
52. Emily Turner, BM BCh1 .Matthew Jones, PhD1 Luis R. Vaz, Tim Coleman, SYSTEMATIC REVIEW AND META-ANALYSIS TO ASSESS THE SAFETY OF BUPROPRION AND VARENICLINE IN PREGNANCY,(2018)
53. Rafaela Costaa , Nuno G. Oliveirab and Ricardo Jorge Dinis-Oliveiraa,c,d, Pharmacokinetic and pharmacodynamic of bupropion: integrative overview of relevant clinical and forensic aspect(2019)
54. Jiaqi Xiongb, Kayla M. Teopizc , Jason Ngd Efficacy of dextromethorphan for the treatment of depression: a systematic review of preclinical and clinical trials Amna Majeeda ,(2021)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