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Dextromethorphan: An update on its utility for neurological and neuropsychiatric disorders

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ABSTRACT

Dextromethorphan (DM) is a commonly used antitussive and is currently the only FDA-approved pharmaceutical treatment for pseudobulbar affect. Its safety profile and diverse pharmacologic actions in the central nervous system have stimulated new interest for repurposing it. Numerous preclinical investigations and many open-label or blinded clinical studies have demonstrated its beneficial effects across a variety of neurological and psychiatric disorders. However, the optimal dose and safety of chronic dosing are not fully known. This review summarizes the preclinical and clinical effects of DM and its putative mechanisms of action, focusing on depression, stroke, traumatic brain injury, seizure, pain, methotrexate neurotoxicity, Parkinson's disease and autism. Moreover, we offer suggestions for future research with DM to advance the treatment for these and other neurological and psychiatric disorders.

Contents

Abbreviations: AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; AMPA, alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; AP-1, activator protein 1; ASD, autism spectrum disorder; AUC, area under the curve; Bay K8644, methyl 2,6-dimethyl-5-nitro-4-[2-(trifluoromethyl)phenyl]-1,4-dihydropyridine-3-carboxylate; BD1047, N′-[2-(3,4-dichlorophenyl)ethyl]-N,N,N′-trimethylethane-1,2-diamine; BDNF, brain derived neurotrophic factor; Cmax, maximum concentration; CNS, central nervous system; CPP, conditioned place preference; CSD, cortical spreading depolarization; CSF, cerebral spinal fluid; CYP, cytochrome P450; dB, decibel; DA, dopamine; DF, dimemorfan; DM, dextromethorphan; DX, dextrorphan; EEG, electroencephalography; EM, extensive metabolizer; EMA, European Medicines Agency; ERK5, extracellular regulated kinase 5; FDA, Food and Drug Administration; FRA-IR, Fos-related antigens immunoreactivity; FST, forced swim test; GABA, gamma-aminobutyric acid; 3-HM, 3-hydroxymorphinan; 5-HT, serotonin; IL, interleukin; IM, intermediate metabolizer; i.p., intraperitoneal; KA, kainate; LPS, lipopolysaccharide; LTP, long-term potentiation; MDD, major depressive disorder; MK801, (5R,10S)-(+)-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine; 3MM, 3-methoxymorphinan; M3G, morphine-3-glucoronide; M6G, morphine-6-glucuronide; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MRI, magnetic resonance imaging; MS, multiple sclerosis; NE, norepinephrine; NET, norepinephrine transporter; NMDA, N-methyl-D-aspartate; NTS, nucleus tractus solitarius; OTC, over-the-counter; PBA, pseudobulbar affect; PCP, phencyclidine; PFC, prefrontal cortex; PD, Parkinson's disease; PDD, pervasive developmental disorder; PM, poor metabolizer; PTZ, pentylenetetrazol; ROS, reactive oxygen species; SERT, serotonin transporter; SNL, spinal nerve ligation; SSRI, selective serotonin reuptake inhibitor; TBI, traumatic brain injury; TMT, trimethyltin; TNF, tumor necrosis factor; TrkA, tropomyosin receptor kinase A; TrkB, tropomyosin receptor kinase B; UM, ultrarapid metabolizer; VGCC, voltage gated calcium channel; VPA, valproic acid.

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1. Introduction

Dextromethorphan (DM) has been a widely used non-opioid antitussive for over 50 years. It was first developed as one of two enantiomers of methorphan, a morphine derivative. DM is available in many over-the-counter (OTC) cough and cold preparations worldwide and does not possess the same central nervous system (CNS) pharmacodynamic effects as other opioids in humans (i.e., analgesia, respiratory depression, addiction or psychotomimetic properties) when taken at therapeutic doses (60–120 mg/day in divided doses). At high doses (from 5 to over 10 times the label-specified maximum dosages), it acts as a dissociative agent similar to the N-methyl-D-aspartate (NMDA) antagonists ketamine and phencyclidine (PCP) (Romanelli & Smith, 2009; Schwartz, 2005; Banken & Foster, 2008). The levorotatory enantiomer of DM, levomethorphan, in contrast, is a low potency opiate analgesic, strictly controlled as a narcotic drug.

Over the past 20 years, accumulating evidence suggests that DM has both anticonvulsant and neuroprotective effects in numerous experimental models of seizure, traumatic brain injury (TBI), stroke, pain, and others (Tortella et al., 1989; Werling et al., 2007b; Shin et al., 2011). Moreover, DM in combination with quinidine, a cytochrome P450 (CYP) 2D6 inhibitor, was recently approved by the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of pseudobulbar affect (PBA). Currently, DM is being used in clinical trials for a variety of CNS-related disorders. As more data is obtained on the use of DM in preclinical and clinical trials, questions about mechanisms of action and potential repurposing avenues for this relatively safe drug take on considerable significance.

In this review, a brief overview is given on the pharmacokinetic and pharmacodynamic properties of DM. We also discuss the currently approved indications for DM, followed by its therapeutic potential in a multitude of neurological and neuropsychiatric disorders. For the disorders mentioned herein, we will elaborate on the putative mechanisms of action underlying the effects of DM. Together, the literature suggests that DM not only has many potential therapeutic applications, but also serves as a promising tool in the development of future medical therapies.

2. Pharmacokinetics and metabolism

DM is commonly used as a probe drug for CYP2D6 metabolizer status. It undergoes extensive first-pass hepatic metabolism via O-demethylation to form its active metabolite, dextrorphan (DX) (Capon et al., 1996; Yu & Haining, 2001). DM is also metabolized to a relatively inactive metabolite, 3-methoxymorphinan (3-MM), via CYP3A4 N-demethylation (Yu & Haining, 2001). These DX and 3-MM metabolites can both undergo further metabolism to another relatively inactive 3-hydroxymorphinan (3-HM) secondary metabolite via CYP3A4 and CYP2D6 demethylation, respectively (Yu & Haining, 2001). However, there is minimal free DX available for metabolism since this active metabolite is rapidly glucuronidated and excreted in urine (Pope et al., 2004). A summary of the metabolic pathway for DM is shown in Fig. 1. DM and DX are both metabolized by CYP2D6, so it is useful to stratify pharmacokinetic comparisons by the four possible CYP2D6 phenotypes: ultrarapid metabolizer (UM), extensive metabolizer (EM), intermediate metabolizer (IM) or poor metabolizer (PM). In a study of 252 Americans, 84.3% were found to be EMs, 6.8% to be IMs, and 8.8% were PMs for DM (Woodworth et al., 1987). In a different study, EM subjects ($N = 6$) given a single oral dose of 30 mg DM demonstrated a median half-life of 2.4 h with an oral bioavailability of 1–2%, while PMs ($N = 6$) had a median half-life of 19.1 h with an oral bioavailability of 80% (Capon et al., 1996). EM subjects also demonstrated a DM median maximum concentration (Cmax) of 1.4 mg/L with an area under the curve (AUC) of 9.0 mg/L·h, while PMs had a median Cmax of 23.0 mg/L with an AUC of 1362 mg/L·h (Capon et al., 1996). After pretreatment with quinidine, a potent CYP2D6 inhibitor, EM subjects demonstrated a DM median Cmax of 24.9 mg/L with an AUC of 383 mg/L·h (Capon et al., 1996). This study demonstrated that PMs may have fourfold higher DM exposure (AUC 1362 vs. 383 mg/L·h, $p < 0.05$), while peak DM plasma concentration (Cmax 23.0 vs. 24.9 mg/L) remained relatively similar when compared to EMs after pretreatment with quinidine.

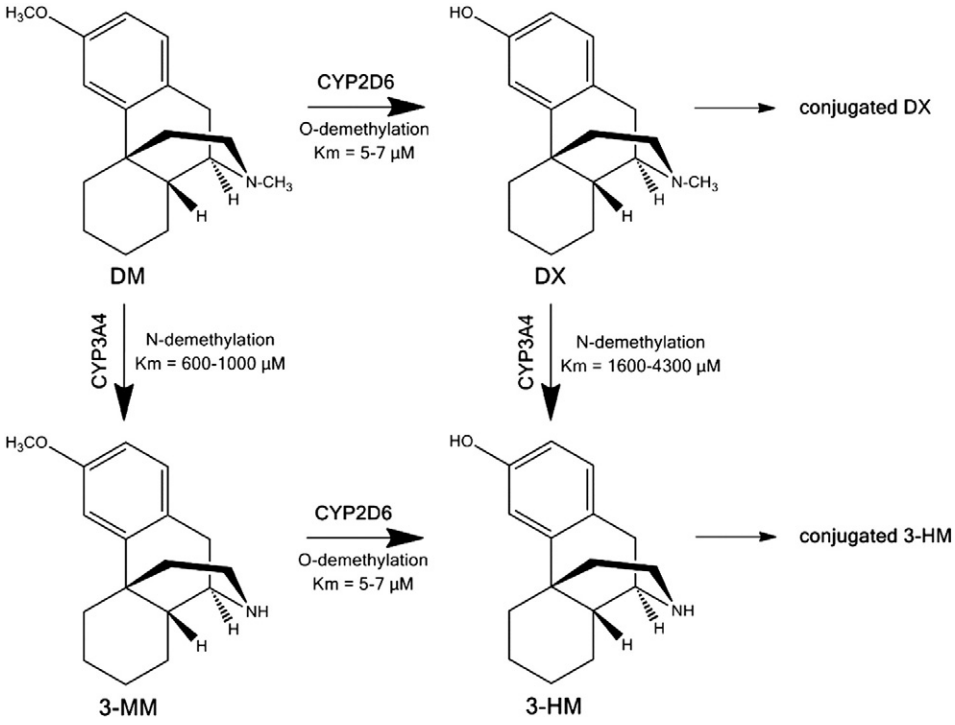

Fig. 1. DM demethylation pathways catalyzed by CYP2D6 and CYP3A4. DX is formed by CYP2D6-mediated O-demethylation of DM. N-demethylation of DM to 3-MM is favored over N-demethylation of DX given the relative Km values for the reactions and the ease with which DX is glucuronidated in vivo. Adapted from Blake et al. (2007). 3-HM, 3-hydroxymorphinan; 3-MM, 3-methoxymorphinan; DM, dextromethorphan; DX, dextrorphan.