



OPEN ACCESS

EDITED BY

Daniel Z. Fan,
Tianjin University of Science and
Technology, China

REVIEWED BY

Davide Amato,
University of Cincinnati, United States
Gohar Fakhfoury,
McGill University, Canada

*CORRESPONDENCE

D. Kavindi Weerasinghe,
✉ dkweerasinghe@deakin.edu.au

RECEIVED 11 March 2023

ACCEPTED 09 May 2023

PUBLISHED 25 May 2023

CITATION

Weerasinghe DK, Hodge JM, Pasco JA,
Samarasinghe RM, Azimi Manavi B and
Williams LJ (2023), Antipsychotic-
induced bone loss: the role of dopamine,
serotonin and adrenergic
receptor signalling.
Front. Cell Dev. Biol. 11:1184550.
doi: 10.3389/fcell.2023.1184550

COPYRIGHT

© 2023 Weerasinghe, Hodge, Pasco,
Samarasinghe, Azimi Manavi and
Williams. This is an open-access article
distributed under the terms of the
[Creative Commons Attribution License
\(CC BY\)](https://creativecommons.org/licenses/by/4.0/). The use, distribution or
reproduction in other forums is
permitted, provided the original author(s)
and the copyright owner(s) are credited
and that the original publication in this
journal is cited, in accordance with
accepted academic practice. No use,
distribution or reproduction is permitted
which does not comply with these terms.

Antipsychotic-induced bone loss: the role of dopamine, serotonin and adrenergic receptor signalling

D. Kavindi Weerasinghe ^{1*}, Jason M. Hodge ^{1,2},
Julie A. Pasco ^{1,2,3}, Rasika M. Samarasinghe ¹,
Behnaz Azimi Manavi ¹ and Lana J. Williams ^{1,2}

¹IMPACT—The Institute for Mental and Physical Health and Clinical Translation, Deakin University, Geelong, VIC, Australia, ²Barwon Health, Geelong, VIC, Australia, ³Department of Medicine—Western Health, The University of Melbourne, Melbourne, VIC, Australia

Antipsychotics are commonly used in treating psychiatric disorders. These medications primarily target dopamine the serotonin receptors, they have some affinity to adrenergic, histamine, glutamate and muscarinic receptors. There is clinical evidence that antipsychotic use decreases BMD and increases fracture risk, with dopamine, serotonin and adrenergic receptor-signalling becoming an increasing area of focus where the presence of these receptors in osteoclasts and osteoblasts have been demonstrated. Osteoclasts and osteoblasts are the most important cells in the bone remodelling and the bone regeneration process where the activity of these cells determine the bone resorption and formation process in order to maintain healthy bone. However, an imbalance in osteoclast and osteoblast activity can lead to decreased BMD and increased fracture risk, which is also believed to be exacerbated by antipsychotics use. Therefore, the aim of this review is to provide an overview of the mechanisms of action of first, second and third generation antipsychotics and the expression profiles of dopamine, serotonin and adrenergic receptors during osteoclastogenesis and osteoblastogenesis.

KEYWORDS

schizophrenia, antipsychotics, osteoclast, osteoblast, bone mineral density, dopamine, serotonin, noradrenaline

1 Introduction

Antipsychotics are the first line treatment in schizophrenia (Lally and MacCabe, 2015). Schizophrenia is a state whereby patients lose connection with reality. This can be in the form of hallucinations, delusions and disorder of thoughts with far-reaching effects on individuals, their families and society (Howes et al., 2009; Patel et al., 2014). Global statistics has shown that schizophrenia is the eighth leading cause of disability in people aged 15–44 years (Haddad and Correll, 2018). Antipsychotics are also used off-label in the treatment of anxiety, borderline personality disorder, substance use disorders, eating disorders, post-traumatic stress disorder, obsessive-compulsive disorder, mood disorders, insomnia, agitation and attention deficit hyperactivity disorder (Wang et al., 2021a; Azimi Manavi et al., 2023). Between 2005–2014, the prescription rate of antipsychotic use overall has increased in 10 out of 16 countries, with the atypical antipsychotics, quetiapine, olanzapine and risperidone being most

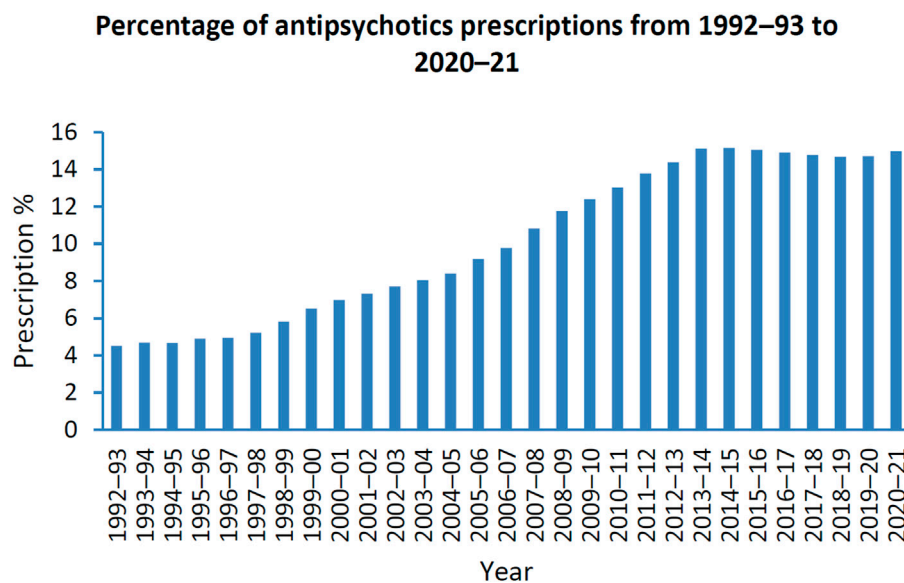


FIGURE 1

Percentage of patients prescribed antipsychotics from 1992–1993 to 2020–2021; Data adopted from mental health services in Australia: Mental health related prescriptions Australian Institute of Health and Welfare (Australian Institute of Health and Welfare, 2022).

prescribed (Hálfðánarson et al., 2017). The Australian Institute of Health and Welfare has reported that 17.7% of Australians received mental health-related medications between 2020 and 2021 where the highest prescription rates were 8.9% and 8.7% for antidepressants and antipsychotics, respectively (Australian Institute of Health and Welfare, 2022). Moreover, the prescription of antipsychotics has increased by 10.5% from 1992-93 to 2020-21 (Australian Institute of Health and Welfare, 2022) (Figure 1).

The use of antipsychotics is associated with a number of side effects including tardive dyskinesia (repetitive, involuntary movements commonly in areas of the face, eyes, and mouth), dystonia (involuntary muscle movements that can affect the head, face, and neck), akathisia (inability to remain still), weight gain, hyperglycaemia, type 2 diabetes and adverse cardiovascular impacts including sudden cardiac death (De Hert et al., 2011). There is a growing body of evidence suggesting that antipsychotics are also associated with negative, off-target side effects that include reductions in bone mineral density (BMD) and increased fracture risk (Kishimoto et al., 2008; Crews and Howes, 2012; Fraser et al., 2015; Bolton et al., 2017; May et al., 2019; Paschou et al., 2019; Azimi Manavi et al., 2023). The mechanism(s) by which antipsychotics induce bone loss are yet to be fully explored and understood. This has led to an emerging area of research to understand the underlying mechanisms by which antipsychotics negatively impact bone.

Bone is a multicellular organ consisting of different cell types, namely: osteoclasts, osteoblasts, osteocytes, chondrocytes, bone lining cells, and bone-resident macrophages known as osteal macrophages or osteomacs (Flores-Silva et al., 2015; Miron and Bosshardt, 2016; Kenkre and Bassett, 2018; Mohamad et al., 2021). Old and damaged bone is resorbed by osteoclasts while new bone is

formed by osteoblasts, which, when entombed in newly formed bone become osteocytes, the most prevalent cells in bone tissue (~90–95%) that act as a master regulator of osteoclast and osteoblast function (Metzger and Narayanan, 2019). Chondrocytes form the cartilage matrix which is later replaced by osteoblasts to undergo endochondral ossification (Chen et al., 2021), while resting osteoblasts are known as bone lining cells (Lee et al., 2021). Osteomacs also regulate bone modelling and remodelling by acting as potential osteoclast precursors and secreting oncostatin M to promote bone formation by osteoblasts (Walker et al., 2010; Mohamad et al., 2021; Hioki et al., 2022). The fine balance between osteoclast and osteoblast activity is central to maintaining normal bone homeostasis and resultant healthy bone (Flores-Silva et al., 2015).

Antipsychotics target different receptors including dopamine, serotonin and adrenergic receptors, which are predominantly located in the brain, but have recently been shown to be present in osteoclasts and osteoblasts (Aringhieri et al., 2018). Therefore, this review summarises commonly prescribed antipsychotics and details their mechanisms of action, in addition to how they may influence various dopamine, serotonin and adrenergic receptors shown to be expressed in osteoclasts and osteoblasts that may ultimately lead to bone loss.

2 Antipsychotics

Initially, antipsychotics categorised as either “typical” or “atypical.” This has changed first-generation antipsychotics (FGA), second-generation antipsychotics (SGA) and third-generation antipsychotics (TGA). These categories are primarily based on their affinity to dopamine and serotonin receptors, where

TABLE 1 Receptor binding profiles for commonly prescribed antipsychotics.

Antipsychotics	Therapeutic plasma level	D ₁	D ₂	D ₃	D ₄	5HT _{1A}	5HT _{1B}	5HT _{2A}	5HT _{2B}	5HT _{2C}	5HT ₆	5HT ₇	Adra1	Adra2a	Adra2b	Adra2c	Adrb2	H1	H2	H3	M1	M3	
(A) Receptor binding profiles for commonly prescribed first generation antipsychotics																							
FGA	Chlorpromazine	23–600 ng/mL Chetty and Miller. (1991)	++	+++	+++	+++			+++	+++	++	+++	+++	+	++	++	?	+++	+	+	++	++	
	Haloperidol	2–12 ng/mL Van Putten et al. (199). Above 18 ng/mL counter therapeutic Coryell et al. (1998)	+	+++	+++	+++		+	+				+	++	+	+	+			+			
	Periciazine	1–5 nmol/L Omérov et al. (1989)	+	++++			+		+++		+		++	+				+++					
	Loxapine	—	++	+++	++	++		+	+++		++	++	++										
	Zuclopenthixol	—		+++														+++					
	Flupentixol	—																					
	Trifluoperazine	0.53–3.09 ng/mL Midha et al. (1983)		+++	++++	++	+		++		+	+	+										
	Perphenazine	1–5 nmol/L Omérov et al. (1989)	?	++++			+		+++		+	++	++										
	Thiothixene	—	++	+++	+	+++	+	+	++			+	++										
(B) Receptor binding profiles for commonly prescribed second generation antipsychotics																							
SGA	Clozapine	350–420 ng/mL Papola et al. (2018)	+	+	+	++	+	+	++	+++	++	++	++	+++	++	++	++		+++	+		+++	++
	Olanzapine	20–80 ng/mL May et al. (2019)	++	++	++	++		+	+++	++	++	+++	++	++	+	++	++		+++	++	+	++	++
	Quetiapine	100–500 ng/mL Houseknecht et al. (2017)	+	+	+		++		++		+	+	++	++	+	++	++		+++			+	+
	Amisulpride	100–319 ng/mL Kawamura et al. (2011)		+++	+++	+++			++			++											
	Risperidone	20–60 ng/mL Papola et al. (2018)	+	+++	+++	+++	+	++	++++	++	++		+++	+++	++	++	+++		+++	+			
	Lurasidone	No data available	+	+++	?		+++		+++		+		++++	++	++		+++		?				
	Ziprasidone	50–130 ng/mL Stubbs et al. (2015)	++	+++	++	+	++	+++	+++	++	++	+++	+++						+++			+	
	Paliperidone	20–60 ng/mL Cohen et al. (2019)	+	+++			+		+++		++		+++						+++			+	
	Iloperidone	>4 ng/mL provide clinical efficacy ClinicalTrials.gov. (2014)	+	+++	+++	++	+		+++		++	++	+	+++		++			+				
	Asenapine	—	+++	+++	++++	+++	+++	+++	+++	++++	++++	++++	+++						+++				
(C) Receptor binding profiles for commonly prescribed third generation and other antipsychotics																							
TGA	Aripiprazole	150–300 ng/mL Lahdelma et al. (2010)		+++	+++	++	+++	+	+++	++++	++		++	++	++	++	++		++				
	Cariprazine	—		+++	+++		+++	?	++	++++	+	?	+	+					++			?	
	Brexipiprazole	—		+++	+++		+++		+++	+++	++		+++	+++	?	?	+++		++			+	

(Continued on following page)

they act as

TABLE 1 (Continued) Receptor binding profiles for commonly prescribed antipsychotics.

Antipsychotics	Therapeutic plasma level	TAAR ₁	D ₁	D ₂	D ₃	D ₄	5HT _{1A}	5HT _{1B}	5HT _{2A}	5HT _{2B}	5HT _{2C}	5HT ₆	5HT ₇	Adra1	Adra2a	Adra2b	Adra2c	Adrb2	H1	H2	H3	M1	M3
Other	0.4–6.0 ng/mL, Mestl et al. (2012); Li et al. (2019)			+++	+++	+++																	
Uloparont	Undergoing clinical trials	?					?																

Antagonism and inverse agonism are indicated by blue, agonism by green and partial agonism by yellow. Data taken from (34,64,140–142,147–184). Binding affinity for receptors: + = weak association (K_i value 100–1,000); ++ = Moderate association (10–91); +++ = strong association (Howes et al., 2009; De Hert et al., 2011; Patel et al., 2014; Fraser et al., 2015; Lally and MacCabe, 2015; Häfslidmarsson et al., 2017; Haddad and Correll, 2018; Wang et al., 2021a; Australian Institute of Health and Welfare, 2022; Azimi Manavi et al., 2023); ++++ = very strong association (K_i < 1); ? = unknown.

TAAR1 = Trace amine associated receptor 1, D = Dopamine receptor, 5HT = Serotonin receptor, Adr = Adrenergic receptor, H = Histamine receptor, M = Muscarinic receptor.

either agonist, partial agonist, antagonist or an inverse agonist (Strange, 2008). First generation antipsychotics are dopamine D₂ (D₂) antagonists, which have been effective in the treatment of positive symptoms while less effective in the treatment of negative symptoms (Mailman and Murthy, 2010; Li et al., 2016). Positive symptoms include hallucinations, delusions and disorder of thoughts while the negative symptoms cause dysfunction in personal, social and occupational functioning through means such as anhedonia, avolition and social withdrawal, as well as, cognitive dysfunction (Winship et al., 2019). The first generation antipsychotic “chlorpromazine” was the first to be recognised as a psychotropic drug in 1952 by Henri Laborit (Laborit et al., 1952; Ban, 2007). Following chlorpromazine, other FGAs including haloperidol, trifluoperazine, thioridazine and fluphenazine were introduced (Ramachandriah et al., 2009). First generation antipsychotics are associated with a number of undesirable side effects including hyperprolactinemia, sedation, weight gain, autonomic and cardiovascular effects, akathisia, parkinsonism, dystonia and tardive dyskinesia (Mailman and Murthy, 2010), thus, spurring on the development of second generation antipsychotics. Second generation antipsychotics are D₂ and serotonin (5HT) antagonists with affinity ratio greater than 1.12 for D₂/5HT_{2A} which have been more effective in reducing negative and cognitive symptoms compared to FGAs, but associated with greater weight gain and metabolic syndromes such as hypertriglyceridemia, elevated glucose, insulin and low-density lipoprotein cholesterol levels (Lieberman, 2004; Mailman and Murthy, 2010; Pillinger et al., 2020; Kiss et al., 2022). A third generation of antipsychotics such as aripiprazole, cariprazine and brexpiprazole were introduced most recently and have been successful in treating positive, negative and cognitive symptoms (Vasiliiu, 2022). These predominantly act as pre-synaptic and post-synaptic D₂ partial agonists rather than receptor antagonists, as well as D₃ and 5HT_{1A} partial agonists, while simultaneously acting as a serotonin 5HT_{2A} and 5HT_{2B} antagonist (Li et al., 2016; Kiss et al., 2022). Current research is focusing on D₃ targeting antipsychotics due to their higher affinity for dopamine than D₂ receptors (Maramai et al., 2016). Moreover, D₃ are predominantly expressed in the limbic system, which is involved in schizophrenia pathology (Kiss et al., 2022) and the blockage of the D₃ is associated with pro-cognitive effects in rats (Watson et al., 2012). As shown in Table 1, antipsychotics possess affinity to other receptors including adrenergic, histamine and muscarinic receptors (Table 1).

3 Schizophrenia and bone health: epidemiological findings

There is a growing body of evidence to show that schizophrenia is associated with osteoporosis, a degenerative bone disease characterised by low BMD and increased fracture risk (Jung et al., 2011; Lally, 2020; Forns et al., 2021; Azimi Manavi et al., 2023). The onset of schizophrenia occurs primarily in adolescents and young adults, where peak bone mass is yet to be achieved (Forns et al., 2021; Zhu and Zheng, 2021). Patients with schizophrenia are possibly vulnerable to bone defects due to lifestyle factors such as a reduced physical activity, smoking, alcohol consumption, vitamin D

deficiency and poor dietary habits in addition to genetic and biological factors (Coentre et al., 2009). A study has shown that smoking and alcohol consumption also leads to further reduced BMD in patients with schizophrenia compared to those who do not smoke or drink alcohol (Jung et al., 2011). Moreover, studies show that the use of antipsychotics further exacerbates bone loss and fracture risk in patients with schizophrenia (Oderda et al., 2012; Rigler et al., 2013; Fraser et al., 2015; Bolton et al., 2017; May et al., 2019; Paschou et al., 2019; Shen et al., 2019). Similarly, studies have shown that increased bone fractures are linked with schizophrenia compared to controls (Tsai et al., 2014; Stubbs et al., 2015; Tseng et al., 2015).

4 Antipsychotic use and bone health: epidemiological, *in vitro* and *in vivo* findings

Epidemiological evidence is growing to suggest antipsychotic use (independent of schizophrenia) is associated with lower BMD, increased fracture risk (Oderda et al., 2012; Rigler et al., 2013; Fraser et al., 2015; Bolton et al., 2017; May et al., 2019; Paschou et al., 2019; Shen et al., 2019; Azimi Manavi et al., 2023) and occurrence of re-fracture (Shen et al., 2019). Some studies suggest typical antipsychotics have a higher fracture risk compared to atypical antipsychotics (Ching-Min et al., 2020), while others suggest there is no difference with regards to the type of antipsychotics and associated fracture risk (May et al., 2019; Shen et al., 2019). Risperidone has been shown to reduce BMD in children and young adults (Calarge et al., 2010; Rosenbloom, 2010) with a significant decrease in BMD compared to olanzapine or other SGAs (Becker et al., 2003; Clapham et al., 2020). It has been reported that patients receiving either FGAs or SGAs are at higher fracture risk as antipsychotics in these categories such as chlorpromazine, risperidone and zotepine increased incident fracture, as well as, re-fracture (Ching-Min et al., 2020). A meta study concluded that FGA users show a 77% increase in hip fractures compared to non-users, while SGA users show a 41% increase. This study also noted that associated fracture risk is 29%, 46%, 49% and 94% for risperidone, olanzapine, quetiapine and haloperidol, respectively (Papola et al., 2018; Shen et al., 2019). Interestingly, research has shown that antipsychotics can accumulate up to 15-fold higher concentration in bone marrow compared to plasma (Houseknecht et al., 2017; May et al., 2019).

Evidence from *in-vitro* (Lahdelma et al., 2010; Kawamura et al., 2011; Motyl et al., 2012; Li et al., 2019) and *in-vivo* bone models (Oh-ie et al., 2002; Kunimatsu et al., 2010; Kawamura et al., 2011; Motyl et al., 2012) support these findings. In experiments conducted in rat primary cells, clozapine inhibited osteoblast mitogenesis and differentiation, as well as, osteoclast formation, whereas haloperidol had no effect (Costa et al., 2011). In mouse bone marrow mesenchymal stem cells (BMSCs), chlorpromazine inhibited osteoclastogenesis via inhibiting the intracellular calmodulin pathway (Kawamura et al., 2011). Risperidone significantly stimulated osteoclast differentiation without affecting osteoblast differentiation (Motyl et al., 2012). *In vitro* studies on antipsychotic-related bone defects in primary human cells are scant. A study showed clozapine has cytotoxic effects on primary cultures

of human BMSCs (Lahdelma et al., 2010). A study using the human osteoblast cell line hFob1.19 showed that risperidone, amisulpride, olanzapine and aripiprazole inhibited osteoblasts cell viability and caused apoptosis in a dose dependent manner (Li et al., 2019).

In vivo evidence has similarly shown negative effects of antipsychotics on bone. Risperidone reduced trabecular and cortical bone mass in mice with increased osteoclast differentiation and resorption using bone marrow derived cells (Motyl et al., 2012). Chlorpromazine and haloperidol have also been shown to decrease BMD in trabecular bone of mice via increased resorption (Oh-ie et al., 2002; Kunimatsu et al., 2010). However, this induced bone loss through dopamine blockers is considered to be rodent specific (Kunimatsu et al., 2010). Clozapine, but not haloperidol, decreased BMD *in-vivo* in mice and reduced osteoclast and osteoblast activity *in-vitro* (Kawamura et al., 2011). Chlorpromazine also reduce osteoclast formation and osteoclastic gene expression in mouse BMSCs (Lahdelma et al., 2010).

5 Antipsychotics and bone cell function: importance of dopamine receptors/signalling in osteoclasts and osteoblasts

Dopamine is a neurotransmitter that controls sleep, motivation, reward, attention, voluntary movements, vision, hormonal regulation and motor functions (Hornykiewicz, 2017; Yang and Tsai, 2017; Wang et al., 2020). Abnormalities in the dopamine system are associated with schizophrenia and psychosis, where positive symptoms are linked with increased dopamine levels in the mesolimbic pathway associated with dopamine D₂ hyperactivity (McCutcheon et al., 2018; Stahl, 2018; McCutcheon et al., 2019). Accordingly, most antipsychotics have been developed to target dopamine D₂. Decreased levels of dopamine in cortical pathway has also been observed using PET scanning in patients with schizophrenia, which needs further study as it is believed that hypo-activity of the mesocortical pathway is associated with negative and cognitive symptoms in schizophrenia (Li et al., 2016; Weinstein et al., 2017). Even though this theory has been accepted for decades, recent data indicate the involvement of dorsal striatum in pathophysiology of schizophrenia (McCutcheon et al., 2019).

Dopamine receptors are G-protein-coupled receptors (GPCR), which belongs to GPCR alpha subunits G_s (stimulatory receptors) and G_i (inhibitory receptors) (Zhang and Shi, 2016; Martel and Gatti McArthur, 2020). There are five dopamine receptors, which are sub-categorised as D₁- and D₂-like, depending on pharmacology and ability to regulate cyclic adenosine monophosphate (cAMP) (Martel and Gatti McArthur, 2020). Dopamine D₁ and D₅ belong to D₁-like receptors that modulate signalling pathways via G_s and increase cAMP production while D₂, D₃ and D₄ belong to D₂-like receptors that modulate via G_i and inhibit cAMP production (Figure 2) (Neve et al., 2004; Martel and Gatti McArthur, 2020). Moreover, D₂-like receptors have 10- to 100-fold higher affinity for dopamine than D₁-like receptors (Martel and Gatti McArthur, 2020). This leads to the assumption that extracellular dopamine levels or changes to dopamine levels from antipsychotic use may have different impacts on D₂-like receptors compared to D₁-like receptor

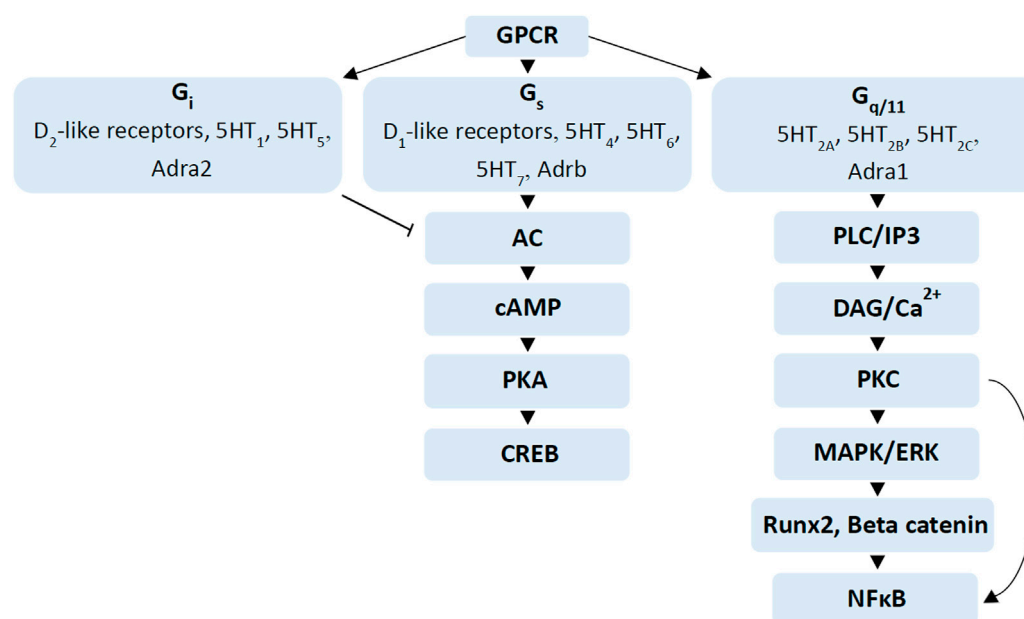


FIGURE 2

Signalling cascades regulated by dopamine, serotonin and adrenergic receptors. G-protein coupled receptor stimulation by different neurotransmitters such as dopamine, serotonin and adrenergic receptors regulate different signalling cascades. Activation of G_i receptors such as D_2 -like receptors, $5HT_1$, $5HT_5$ and Adra2 inhibit adenylate cyclase (AC), while activation of G_s receptors such as D_1 -like receptors, $5HT_4$, $5HT_6$, $5HT_7$ and Adrb stimulate AC to increase cAMP levels, which in turn activate the PKA/CREB pathway (Zhao et al., 2016; Ramaswamy et al., 2017; Wang et al., 2018; Martel and Gatti McArthur, 2020). $G_{q/11}$ receptors activate PLC-IP3 and DAG-PKC signalling pathways, which activate the mitogen-activated protein kinase (MAPK)/ERK signalling cascade (Gustafsson et al., 2006a; Dai et al., 2014; McCorvy and Roth, 2015). Activation of MAPK/ERK also stimulates Runx2 and beta-catenin in osteogenesis while activation of Protein kinase C (PKC) stimulates nuclear factor kappa-light-chain-enhancer of activated B cells (NFkB), important in osteoclast differentiation (Abu-Amer, 2013; Zhao et al., 2016; Kim et al., 2019).

signalling (Martel and Gatti McArthur, 2020). Dopamine has been found in bone marrow in higher concentrations ($\sim 10 \mu\text{M}$) than typically found in circulation (Matt and Gaskill, 2020). Moreover, hypothalamic neurons produce dopamine to regulate bone metabolism via hypothalamic-pituitary-gonadal axis while sympathetic nerves also contain dopamine which can penetrate to bone marrow (Wang et al., 2021b).

5.1 Dopamine signalling in osteoclasts

Dopamine has been demonstrated to inhibit osteoclastogenesis in a dose-dependent manner using osteoclast precursors derived from: i) human $CD14^+$ cells isolated from peripheral blood mononuclear cells (PBMCs) (Hanami et al., 2013); ii) murine BMSCs (Yang et al., 2016); and iii) RAW 264.7 cells (Wang et al., 2021b). There are limited studies showing links between dopamine and bone cell function. Studies have reported that dopamine can interact with receptors in osteoclasts derived from human BMSCs to inhibit resorption via nuclear factor of activated T-cells cytoplasmic 1 (NFATc-1) and c-Fos signalling pathways (Hanami et al., 2013; Wang et al., 2020). Hanami et al. (2013) showed that dopamine D_2 -like signalling inhibits osteoclastogenesis *in-vitro*, which could be a protective mechanism against bone resorption while Wang et al. (2021) showed that dopamine inhibits osteoclastogenesis via D_2R /cAMP/protein kinase A (PKA)/cAMP response element-binding protein (CREB) pathway

in primary mice BMSCs (Wang et al., 2021b). In contrast, it has been shown that D_1 -like receptor antagonist SCH23390 inhibits osteoclastogenesis in mice bone marrow-derived macrophages (Nakashioya et al., 2011).

Expression of dopamine receptors in osteoclast has been reported in a number of animal and human models (Table 2). The presence of all five dopamine receptors and the dopamine transporter (DAT) have been reported in human $CD14^+$ monocytes at both transcriptional and protein levels (Gaskill et al., 2012; Hanami et al., 2013). Maximum expression was observed in the early stages of osteoclastogenesis, decreasing after day 7 (Hanami et al., 2013). Similarly, all five dopamine receptors were identified in RAW 264.7 cells and in primary mice bone marrow derived macrophage-lineage cells from C57BL/6J mice (Wang et al., 2021b), in addition to mouse BMSCs, where increased expression of D_1 , D_2 and D_3 was observed during osteoclastogenesis (Cheong et al., 2018).

5.2 Dopamine signalling in osteoblasts

The effects of dopamine on osteoblasts is more contentious. A study by Lee et al. (2015) reported that dopamine enhances osteoblast proliferation and mineralisation *in-vitro* in a MC3T3-E1 pre-osteoblastic murine cell line (Lee et al., 2015), while another study by Motyl et al. (2017) directly refuted these findings, reporting suppression of osteoblast mineralisation and osteoblast markers of

TABLE 2 Dopamine receptor expression in osteoclasts and osteoblasts.

Type of dopamine receptor	Experiment cell type	References
Osteoclasts (OC)		
D ₁ , D ₂ , D ₃ , D ₄ and D ₅	RAW 264.7 cells	Wang et al. (2021b)
D ₁ , D ₂ , D ₃ , D ₄ and D ₅	Primary mice BM cells	Berger et al. (2009), Motyl et al. (2017), Cheong et al. (2018), Wang et al. (2021b)
D ₁ , D ₂ , D ₃ , D ₄ , D ₅ and DAT	Human PBMC derived CD14 ⁺ cells	Gaskill et al. (2012), Hanami et al. (2013), Wysokiński et al. (2021)
Osteoblasts (OB)		
D ₁ , D ₂ , D ₃ , D ₄ and D ₅	MC3T3-E1 cells	Lee et al. (2015), Motyl et al. (2017), Zhu et al. (2022)
D ₁ and D ₂	Rat BMSCs	Cheong et al. (2018), Wang et al. (2020)
D ₁ , D ₂ , D ₃ , D ₄ and D ₅	Mice primary BM derived OB	Motyl et al. (2017), Handa et al. (2019)
D ₁ and D ₂	Human BMSCs	Wang et al. (2020)

gene expression (Motyl et al., 2017). The expression of all five dopamine receptors in osteoblasts has been shown at both mRNA and protein levels in MC3T3-E1 cells (Lee et al., 2015; Zhu et al., 2022). Dopamine (50 μ M) did not affect osteoblast cell proliferation but increased mineralisation, compared to control, whereas concentrations above 100 μ M induced cell death (Lee et al., 2015). Bone marrow mesenchymal stem cells can be differentiated into cartilage, tendon, muscle, fat and osteoblasts (Caplan, 1991; Pittenger et al., 1999; Sacchetti et al., 2007; Méndez-Ferrer et al., 2010; Wang et al., 2020). Primary murine BMSCs-derived osteoblasts express dopamine receptors, which regulate proliferation and differentiation (Motyl et al., 2017; Cheong et al., 2018; Handa et al., 2019; Wang et al., 2020). The expression of D₁ and D₂ was significantly increased from day 3 to day 7 in rat BMSCs (Wang et al., 2020). Wang et al. (2020) showed the presence of dopamine receptors D₁ and D₂ in human BMSCs where the expression of D₁ increased until day 5 and the expression of D₂ decreased from day three to day 5 (Wang et al., 2020). Moreover, alkaline phosphatase activity (ALP), mineralisation and expression of bone sialoprotein, runt-related transcription factor 2 (Runx2), and osteocalcin were stimulated with dopamine (5 nM). This stimulation was lost at 50 μ M, whereas 500 μ M was toxic (Wang et al., 2020). This study also demonstrated that dopamine-induced osteogenic differentiation of human BMSCs was mediated through D₁ receptor activation via extracellular signal-regulated kinase (ERK) 1 and 2 signalling pathways and activation of Runx2 transcriptional activity, while the suppression of cAMP/PKA pathway may inhibit dopamine-induced human BMSCs differentiation (Wang et al., 2020).

Antipsychotics targeting D₃ receptors have gained more attention in treating impaired cognitive, social, and motor functions associated with schizophrenia. To our knowledge, there are no studies on the effects of D₃ on bone remodelling. Hence, it is important to investigate the effects of D₃ in bone cells function, due to its similarity to D₂, which can also activate ERK/MAPK signalling pathway (Kiss et al., 2022), which is important in bone homeostasis and skeleton development (Kim et al., 2019). Moreover, both D₂ and D₃ activate their signalling cascades in GPCR independent manner via beta arrestin mediated pathways (van Gastel et al., 2018). Studies show that beta arrestin 2 is involved in regulating

MAPK/AKT/glycogen synthase kinase 3 (GSK3) pathways downstream of the dopamine receptors (Del'Guidice et al., 2011). Glycogen synthase kinase 3 is expressed in the brain and important in psychiatric diseases such as schizophrenia (van Gastel et al., 2018). Interestingly, both D₂ and D₃ are positively coupled to beta arrestin/AKT/GSK3 pathway (van Gastel et al., 2018). Beta arrestin 2 stimulates mice trabecular bone formation but not bone resorption indicating the importance of this pathway in bone homeostasis (Gesty-Palmer et al., 2009).

In summary, the presence of all dopamine receptors in osteoclasts has been shown using RAW 264.7, primary mice BMSCs and human CD14⁺ cells where expression increased during osteoclastogenesis (Table 1). The presence of dopamine receptors in osteoblasts has also been shown in MC3T3-E1 (with no difference in expression level for 14 days), rat BMSCs (with increased D₁ and D₂ from day 3 to 7) and human BMSCs (with increased D₁ expression until day 5 while D₂ expression decreased after day 3) (Lee et al., 2015; Wang et al., 2020). It has also been demonstrated that low concentrations of dopamine (5 nM) can increase osteoblast marker expression (Wang et al., 2020). Moreover, dopamine regulates osteoclastogenesis via nuclear factor of activated T Cells 1 (NFATc1), cFOS, cAMP/PKA/CREB via D₂ receptor while dopamine regulates osteoblastogenesis via ERK 1 and 2, Runx2 and cAMP/PKA via the D₁ receptor (Wang et al., 2020; Wang et al., 2021b). However, there is limited data available on the effect of dopamine on human models. As all antipsychotics primarily target dopamine receptors as antagonists or partial agonists it is important to understand the dopamine receptor expression profile in bone cells to understand the complex mechanism of antipsychotics-induced bone loss.

6 Antipsychotics and bone cell function: importance of serotonin receptors/signalling in osteoclasts and osteoblasts

Serotonin is a product of tryptophan metabolism and is produced both in the central nervous system and peripherally in gastrointestinal tract and in platelets, where it does not cross the

blood brain barrier (Brenner et al., 2007; Kanova and Kohout, 2021). Peripheral serotonin accounts for the majority of serotonin produced in the body (~95%), while the brain is responsible for only a minor fraction (Ducy and Karsenty, 2010; El-Merahbi et al., 2015). Centrally, serotonin acts as a neurotransmitter, while peripherally its role is as a hormone (Kanova and Kohout, 2021). As a neurotransmitter, serotonin regulates mood, reward, anger, perception, appetite, aggression, attention, memory and sex drive. Peripherally, serotonin regulates major organ functions including glucose homeostasis and lipid metabolism (Berger et al., 2009; Kanova and Kohout, 2021). It has been reported that serotonin acts centrally to inhibit bone resorption and increase bone formation, whilst peripherally it acts to directly inhibit bone formation (Ducy and Karsenty, 2010; El-Merahbi et al., 2015). It has been reported that osteoclasts can synthesise serotonin in the presence of receptor activator of nuclear factor kappa-B ligand (RANKL). Osteoblast-derived RANKL stimulates the expression of tryptophan hydroxylase 1 (TPH₁) by osteoclasts, which results in serotonin synthesis that may then play a role as a paracrine/autocrine factor to further regulate osteoclast formation and resorption (Chabbi-Achengli et al., 2012).

There are seven types of serotonin receptors, 5HT₁ to 5HT₇, which are all GPCRs, except 5HT₃ (Nichols and Nichols, 2008; McCorvy and Roth, 2015). These receptors modulate different signalling pathways via G_i, guanine nucleotide binding protein alpha 11 (G_{q/11}), and G_s (Figure 2) (McCorvy and Roth, 2015). The receptors 5HT₁ and 5HT₅ belong to the G_i protein-coupled receptors, while the 5HT_{2A}, 5HT_{2B} and 5HT_{2C} receptors belong to the G_{q/11} protein-coupled receptors and 5HT₄, 5HT₆ and 5HT₇ belong to G_s protein-coupled receptors (Dai et al., 2014; McCorvy and Roth, 2015). The G_i protein-coupled receptors 5HT₁ and 5HT₅ suppress the cAMP/PKA pathways, inhibiting bone formation (Yadav et al., 2008; Dai et al., 2014; McCorvy and Roth, 2015). It has also been shown that activation of the cAMP/PKA pathway is associated with increased osteogenesis *in-vitro* and increased bone formation *in-vivo* (Siddappa et al., 2009). In contrast, in OC, the inhibition of PKA leads to the phosphorylation of activating transcription factor 4 (ATF4), which stimulates osteoclast differentiation (Kode et al., 2012). G_{q/11} protein-coupled receptors, 5HT_{2A}, 5HT_{2B} and 5HT_{2C} activate phospholipase C-inositol phosphate 3 (PLC-IP3) and diacylglycerol-protein kinase C (DAG-PKC) signalling pathways, which promote osteoblast differentiation and bone formation while G_s protein-coupled receptors 5HT₄, 5HT₆ and 5HT₇ increase cAMP levels (Gustafsson et al., 2006a; Dai et al., 2014; McCorvy and Roth, 2015).

6.1 Serotonin signalling in osteoclasts

The localisation of serotonin receptors has been extensively reported in animal and human *in-vitro* and *in-vivo* bone cell models, with varying expression profiles of serotonin receptors in osteoclasts (Table 3). Expression of 5HT_{1B}, 5HT_{2A}, 5HT₄ and serotonin transporter (SLC6A4) has been reported in differentiated RAW264.7-derived osteoclasts (Battaglino et al., 2004), while the presence of all serotonin receptors (5HT₁-5HT₇) have been demonstrated in mouse BMSCs, suggesting a role for these receptors in osteoclasts differentiation (Park et al.,

2018). The presence of 5HT_{1B}, 5HT_{2A}, and 5HT_{2B} was shown in osteoclast precursors from mice spleen cells and not 5HT_{1A} and 5HT₄ (Chabbi-Achengli et al., 2012). The expression level changed with RANKL exposure where 5HT_{1B} receptor expression increased and 5HT_{2B} expression decreased with no change in the 5HT_{2A} receptor expression (Chabbi-Achengli et al., 2012). This could suggest that 5HT_{1B} may be important in osteoclast differentiation from precursors to mature osteoclasts while 5HT_{2A} may act before osteoclasts lineage begins (Chabbi-Achengli et al., 2012). Gustafsson et al. (2006) showed the presence of 5HT_{2A}, 5HT_{2B}, 5HT_{2C}, SLC6A4 and TPH₁ but not 5HT_{1A} in human PBMC-derived osteoclasts (Gustafsson et al., 2006b). The presence of 5HT_{1B}, 5HT_{2B}, SLC6A4 and TPH₁ in human umbilical cord blood-derived osteoclast precursors have been shown, while the level of 5HT_{2B} expression increased in mature osteoclasts (Hodge et al., 2013).

Serotonin has been shown to increase osteoclastogenesis by stimulating both osteoclast formation and resorption in human PBMC derived osteoclasts (Gustafsson et al., 2006b). It has been reported that RANKL induces serotonin synthesis in mice osteoclast precursors whereas serotonin synthesis decreased as osteoclasts matured (Chabbi-Achengli et al., 2012). The study by El-Merahbi, Löffler et al. (2015) also found that 5HT_{1B} and 5HT_{2A} are involved in mediating serotonin in osteoclast differentiation. Moreover, selective blockage of 5HT_{1B}, 5HT_{2B} and 5HT₄ did not affect osteoclastogenesis in RAW264.7 cells (Battaglino et al., 2004). In contrast, antagonism at 5HT_{1B} and 5HT₄ in mouse BMSCs-derived osteoclasts inhibit osteoclast marker expression (Battaglino et al., 2004). This may be because RAW264.7 cells are more differentiated than osteoclast precursors used in bone marrow cell preparation, also suggesting the importance of 5HT_{1B} and 5HT₄ in mediating osteoclast differentiation (Battaglino et al., 2004). The osteoclasts activity was inhibited by serotonin or serotonin agonists for 5HT₁, 5HT₄, and 5HT₇, with no effect on osteoclasts activity with 5HT₂ and 5HT₅ agonists in mice BMSCs (Park et al., 2018). Serotonin has been shown to increase osteoclastogenesis at concentrations of 10 μM or below in mice BMSCs derived osteoclasts, with 5HT₆ being more significant (Park et al., 2018). Moreover, it has been reported that mast cells release serotonin locally at high concentration (Battaglino et al., 2004). Mast cells in bone marrow are reported to increase in ovariectomised rats that suffered rapid bone loss (Lesclous et al., 2001). These data suggest that serotonin may modulate osteoclastogenesis *in-vivo*.

6.2 Serotonin signalling in osteoblasts

The expression of SLC6A4, 5HT_{1A}, 5HT_{1B}, 5HT_{1D}, 5HT_{2A}, 5HT_{2B}, 5HT_{2C} and TPH₁ have been reported in primary cultures of rat osteoblasts, in addition to the osteoblastic cell lines; ROS 17/2.8, UMR 106-H5, Py1a, MLO-Y4 and MC3T3-E1, with the highest expression of 5HT_{1B} and 5HT_{2A} observed in both the early and late stages of differentiation (Bliziotis et al., 2001; Dai et al., 2014). The presence of TPH₁ indicates that these cell lines may have the capacity to synthesise serotonin that may subsequently act in a paracrine/autocrine manner on bone cells in the bone remodelling space. Receptor 5HT_{2B} has been demonstrated in fetal chicken bone, where this receptor had the highest mRNA expression in skeleton

TABLE 3 Serotonin receptor expression in osteoclasts and osteoblasts.

Type of serotonin receptor	Experiment cell type	References
Osteoclasts (OC)		
5HT _{1B} , 5HT _{2B} , 5HT ₄ and SLC6A4	RAW264.7	Battaglino et al. (2004)
5HT _{1B} , 5HT _{2A} , and 5HT _{2B} , but not 5HT _{1A} and 5HT ₄	Primary mice spleen cell cultures composed mainly of monocytes/macrophages	Chabbi-Achengli et al. (2012)
5HT ₁ - 5HT ₇	Mice BM derived macrophages	Park et al. (2018)
5HT _{2A} , 5HT _{2B} , and 5HT _{2C} , SLC6A4, and TPH1, but not 5HT _{1A}	Human PBMC	Gustafsson et al. (2006b)
5HT _{1B} , 5HT _{2B} , SLC6A4 and TPH1, but not 5HT _{2A}	Human CBMC	Hodge et al. (2013)
Osteoblasts (OB)		
SLC6A4, 5HT _{1A} , 5HT _{2A} and TPH1	MLO-Y4 and MC3T3-E1	Blizotes et al. (2006)
SLC6A4, 5HT _{1A} , 5HT _{1D} , 5HT _{2A} and 5HT _{2B}	Primary rat OB, ROS 17/2.8, UMR 106-H5, and Py1a	Blizotes et al. (2001)
5HT _{2A} , 5HT _{2B} and 5HT _{2C}	Mouse OB from the limbs (tibiae, femurs, humeri) of adult swiss albino mice	Westbroek et al. (2001)
5HT _{2B}	Fetal chicken calvarial bones	
5HT _{1A} , 5HT _{1B} , 5HT _{2A} and 5HT _{2B} , 5HT ₆	Primary mouse OB	Collet et al. (2008), Yadav et al. (2008), Yun et al. (2016)
5HT _{1A} , 5HT _{1B} , 5HT _{1D} , 5HT _{2A} , 5HT _{2B} 5HT _{2C}	Primary rat OB	Dai et al. (2014)
TPH1, SLC6A4, 5HT _{1B} , 5HT _{2A} and 5HT _{2B}	Primary Human OB from trabecular bone samples	Hodge et al. (2013)

tissue compared to the other tested tissues (Westbroek et al., 2001). The presence of 5HT_{2A}, 5HT_{2B} and 5HT_{2C} also observed in murine osteoblasts, where 5HT_{2A} and 5HT_{2B} had higher mRNA expression compared to 5HT_{2C} (Westbroek et al., 2001). Serotonin decreased osteoblast proliferation and mineralisation from 1 nM to 10 μ M, where there is an increased trend of proliferation and mineralisation after 1 μ M (Dai et al., 2014). Collet et al. (2008) reported 5HT_{2B} receptor expression increased during osteoblast differentiation in bone marrow derived mouse osteoblasts while 5HT_{2B}^{-/-} leads to osteopenic phenotype (Collet et al., 2008). Yadav et al. (2008) also reported the presence of 5HT_{1B}, 5HT_{2A} and 5HT_{2B} receptors in primary mouse osteoblasts and that serotonin inhibited osteoblast proliferation via 5HT_{1B} by inhibiting cAMP/PKA/CREB while there was no effect of 5HT_{2A} and 5HT_{2B} on bone mass (Yadav et al., 2008). In contrast, it has been shown that 5HT_{2B} receptor activation was responsible for increased ALP activity and mineralisation in mice (Baudry et al., 2010). Hodge et al. (2013) reported the presence of TPH1, SLC6A4, 5HT_{1B}, 5HT_{2A} and 5HT_{2B} in mature primary human osteoblasts with the highest expression of TPH₁. Yun et al. (2016) showed that 5HT₁₋₇ expression is higher in bone compared to brain, where the 5HT₆ expression was the highest followed by 5HT₂ in primary mice calvarial osteoblasts where 5HT₆ inhibited osteoblast differentiation via Jab1 in BMP2 signalling but not PKA and ERK1/2 (Yun et al., 2016). This data suggest the possible role of 5HT₆ in regulating abnormal osteoblasts differentiation.

In summary, expression of serotonin receptors has been clearly demonstrated in both animal and human models of osteoclast- and osteoblastogenesis. Receptors 5HT_{1B}, 5HT_{2A}, 5HT_{2B} and 5HT₄ are found to be implicated in regulating osteoclast and osteoblast

activity and more specifically the loss of 5HT_{2B} leads to decreased bone formation (Battaglino et al., 2004; Collet et al., 2008; Baudry et al., 2010; Chabbi-Achengli et al., 2012; Hodge et al., 2013; Park et al., 2018) while 5HT₆ may important in regulating osteoblasts differentiation (Yun et al., 2016). There are relatively few reports available, however, that detail associated signalling pathways downstream of serotonin receptor binding in bone cell function, especially in human models. Therefore, it is important to further investigate serotonin receptor expression profile in human bone cells to better understand antipsychotic-induced bone loss as SGA and TGA have varying affinities to these receptors.

7 Antipsychotics and bone cell function: importance of adrenergic receptors/signalling in osteoclasts and osteoblasts

Adrenergic receptors (adrenoceptors) are GPCRs that are involved in activating neurotransmitters; noradrenaline (norepinephrine) and adrenaline (epinephrine) (Graham, 1990). These receptors are expressed in the peripheral and central nervous system as hetero receptors inhibiting the release of neurotransmitters such as serotonin, gamma-aminobutyric acid (GABA) and dopamine (Cruz Grecco Teixeira et al., 2016). There are two main types of adrenergic receptors; alpha (α) and beta (β), with multiple subtypes. Alpha receptors have subtypes α 1 (Adra1) and α 2 (Adra2) with further sub-categories α 1A (Adra1a), α 1B (Adra1b), α 1D (Adra1d), and α 2A (Adra2a), α 2B (Adra2b),

TABLE 4 Adrenergic receptor expression in osteoclasts and osteoblasts.

Type of adrenergic receptor	Experiment cell type	References
Osteoclasts (OC)		
Adra1a, Adra2a Adra2b and Adra2c	RAW 264.7 cells	Suga et al. (2010), Hamajima et al. (2018)
Adrb2 in mature OC	BM cells collected from male C57BL/6J mice and RAW264.7 cells	Kondo et al. (2013)
Adra2a, Adra2b and Adra2c	Primary BM cells from C57BL/6J mice	Hamajima et al. (2018)
Adra1b, Adra2b and Adrb2	Human BM derived OC- like MNCs	Arai et al. (2003)
Adra1b, Adra2b and Adrb2	Human BM derived OC	Togari (2002)
Osteoblasts (OB)		
Adra1b, Adra1d and Adrb2	MC3T3-E1 osteoblastic cell line	Nishiura and Abe (2007), Moriya et al. (2015)
Adrb1, Adrb2 and Adrb3	Primary mice OB	Ma et al. (2011)
Adrb1, Adrb2 and Adrb3	Female Sprague-Dawley rat condylar subchondral bone	Jiao et al. (2015)
Adra1b, Adrb1, Adrb2 and Adrb3	Human SaM1, SaOS2, HOS and MG63	Togari et al. (1997), Togari (2002)
Adrb1 and Adrb2	Human OB cell line	Khosla et al. (2018)
Adra1b, Adra2a and Adrb2	Trabecular ends of human fetal long bone and MG63 cells	Huang et al. (2009)

α 2C (Adra2c) (Perez, 2020) while beta receptors have subtypes β 1 (Adrb1), β 2 (Adrb2) and β 3 (Adrb3). The Adra1, Adra2 and Adrb modulate signalling pathways through $G_{q/11}$, G_i and G_s , respectively (Figure 2) (Bylund et al., 2013).

7.1 Adrenergic signalling in osteoclasts

Mammalian bone is innervated by sympathetic nerves (Hill and Elde, 1991; Khosla et al., 2018). In normal bone remodelling, noradrenaline is released by sympathetic nerves, which are known to inhibit bone formation and stimulate bone resorption (Khosla et al., 2018). Adrenergic receptor expression has been shown in human osteoclasts and osteoblasts (Table 4). The expression of β -adrenergic receptors have been demonstrated in both osteoclasts and osteoblasts (Kondo et al., 2013). Activation of β -adrenergic receptors regulate the secretion of cytokines by osteoblasts, which indirectly stimulated osteoclast activity in human bone marrow-derived osteoclast-like mononuclear cells (Arai et al., 2003; Zhong and Xia, 2021). Activation of Adrb2 inhibited CREB phosphorylation and subsequent osteoblast proliferation, which result in increased ATF4 phosphorylation and RANKL expression leading to increased osteoclast activity and bone resorption (Elenkov et al., 2001; Kajimura et al., 2011; Zhong and Xia, 2021). It has been suggested that β -adrenergic receptor stimulation may also increase RANKL production by T cells, which also may drive osteoclastogenesis (Elenkov et al., 2001; Bonnet et al., 2008).

Animal studies have shown that β -receptor agonists increase the levels of prostaglandin 2 and interleukin-6 (IL-6), which promotes osteoclast proliferation and resorption in mice skulls, thereby decreasing bone mass (Zhong and Xia, 2021). The mouse osteoclast precursor cell line RAW264.7 expresses Adrb2 and these receptors stimulate osteoclastogenesis via reactive oxygen species production (Zhong and Xia, 2021). The presence of all

three Adra2 receptors in RAW264.7 cells have been reported on days 0, 2 and 4 after administration of RANKL while there was no significant difference in receptor expression between days 0, 2 and 4 (Hamajima et al., 2018). In contrast, in mice primary bone marrow cells, Adra2b showed to be upregulated after RANKL administration while Adra2a and Adra2c expression was significantly downregulated (Hamajima et al., 2018). Similarly, expression of Adrb2, but not Adrb1 and Adrb3, is detected in mature osteoclasts derived from mice BMSCs (Zhong and Xia, 2021). It has also been reported that Adra2 agonists suppress osteoclastic gene expression in RAW264.7 cells and in primary bone marrow cells, namely; NFATc1, tartrate-resistant acid phosphatase (TRAP) and cathepsin K, with a corresponding decrease in TRAP positive multi-nucleated osteoclast number in mouse BMSCs (Hamajima et al., 2018).

7.2 Adrenergic signalling in osteoblasts

Receptor Adrb2 is thought to be the main receptor expressed in sympathetic nerves responsible for the regulation of bone mass via osteoblasts (Zhong and Xia, 2021). Adrb2 negatively impacts bone formation by inhibiting the cAMP/CREB pathway, which is important in osteoblast activity (Dimitri and Rosen, 2017; Zhong and Xia, 2021). It has also been shown that parathyroid hormone (PTH) suppresses Adrb2 expression in the MC3T3-E1 osteoblastic cell line mediating phosphorylation of CREB (Moriya et al., 2015). In bone cells, the major pathway involved in PTH is via cAMP/PKA/CREB where the phosphorylation of CREB upregulates osteoblasts differentiation and bone formation (Zhang et al., 2011). Moreover, in animal studies, Adrb2-deficient mice have shown higher osteoblast activity and high bone mass with decreased resorption (Takeda et al., 2002; Elefteriou et al., 2005; Zhong and Xia, 2021). Other studies have also shown that blocking Adrb2 increases bone mass (Pasco et al., 2004; Sato et al., 2010).

Receptors Adra1b and Adra1d was strongly expressed in MC3T3-E1 cells (Nishiura and Abe, 2007). Likewise, Adra1b and Adrb2 were detected in human osteoblasts and MG63 cells, whereas expression of Adra2a was relatively weak, with low levels of expression of Adra2c only in demonstrated in MG63 cells (Huang et al., 2009). This study also showed the expression of Adra1b to be three-fold higher than Adrb2 expression in human osteoblasts. It has been reported the expression of Adrb1, Adrb2, Adrb3 and Adra1b receptors in human periosteum-derived osteoblastic cells (SaM1) and human osteosarcoma-derived cells: SaOS2, HOS and MG63 (Togari et al., 1997; Togari, 2002).

In human osteoblasts, both Adra1 and Adrb2 agonists stimulate RANKL and soluble decoy RANK receptor osteoprotegerin (OPG) mRNA expression, where Adra1 agonists stimulated proliferation and OPG mRNA expression at lower concentration than required for RANKL stimulation. The Adrb2 agonists predominantly upregulated resorption signals by increasing RANKL expression at lower concentration than required for OPG stimulation. Moreover, beta blockers inhibited Adrb2 induced RANKL mRNA expression, but not OPG mRNA expression (Huang et al., 2009), which could result in higher BMD and protection against fracture, which has also been shown by Pasco et al. (2004) (Pasco et al., 2004). This suggests the possibility that Adra1 and Adrb2 may be intimately involved in regulating bone turnover. It has also suggested that the PKC and ERK signalling pathways may mediate RANKL expression via Adra1 receptors (Huang et al., 2009).

There is a lack of data on adrenergic receptor expression profile in bone cells, particularly in primary human cells, where adrenergic receptors, especially Adrb2, are associated with bone mass regulation. In summary, both osteoclasts and osteoblasts express adrenergic receptors including Adra1b, Adra2a, Adra2b, Adra2c, Adra1d, Adrb1, Adrb2 and Adrb3 (Table 1). Among these receptors, Adrb2 is highly implicated in regulating bone mass, where Adrb2-signaling increases resorption in osteoclasts via prostaglandin 2 and IL-6, while decreasing bone formation via cAMP/PKA/CREB/AP1 signalling leading to overall decrease in bone mass (Kellenberger et al., 1998; Arai et al., 2003; Zhong and Xia, 2021). Moreover, Adra1 also regulates osteoclast resorption via PKC/ERK pathway (Huang et al., 2009).

8 Conclusion

In light of the emerging clinical evidence that schizophrenia and antipsychotics both independently decrease BMD and increase fracture risk, there remains a need to build on the existing evidence identifying the presence of dopamine, serotonin and adrenergic receptors in bone. The evidence to date indicate that dopamine directly inhibits osteoclastogenesis via the D₂/cAMP/PKA/CREB pathway (Wang et al., 2021b). In contrast, dopamine stimulates osteoblastogenesis via the D₁/ERK 1 and 2/Runx2 pathway while inhibition of cAMP/PKA can inhibit dopamine-induced osteogenesis (Wang et al., 2020). Centrally-produced serotonin decreases bone resorption and increases bone

formation. However, in the periphery, serotonin directly acts on osteoblasts to inhibit bone formation (Ducy and Karsenty, 2010). Data indicate that 5HT_{2B} and 5HT₆ play an important role in maintaining bone mass. It has been suggested that bone turnover is regulated by Adrb2 and Adra1 by regulating RANKL and OPG levels (Huang et al., 2009). Further, activation of Adrb2 inhibits CREB phosphorylation leading to decreased osteoblast proliferation and Adrb2 can activate cAMP/PKA/AP1 pathways to regulate bone formation (Kellenberger et al., 1998; Arai et al., 2003; Zhong and Xia, 2021).

Therefore, we assume that antipsychotics may cause imbalance in bone formation and resorption via dopamine, serotonin and adrenergic receptors through cAMP/PKA/CREB, ERK 1/2, AP1 and Jab1/Smad1, 5, 8/BMP2 pathways. Further studies are required in animal and human models of bone formation and resorption to help characterise the role of associated signalling pathways and the direct impact of antipsychotics on different receptors present in bone cells. Given antipsychotics largely target dopamine and serotonin receptors, as well as, albeit to a lesser extent adrenergic receptors, it is important to explore the mechanism(s) of action by which antipsychotics impact bone loss.

Author contributions

DKW drafted this manuscript. All authors contributed to the article and approved the submitted version.

Funding

This work was supported by the National Health and Medical Research Council (NHMRC), Australia (Grant Nos 1162867). DKW and BAM were supported by the Deakin University Postgraduate Research Scholarship (DUPRS) and LW by the NHMRC Emerging Leadership Fellowship (Grant No. 1174060).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

- Abbas, A. I., Hedlund, P. B., Huang, X. P., Tran, T. B., Meltzer, H. Y., and Roth, B. L. (2009). Amisulpride is a potent 5-HT7 antagonist: Relevance for antidepressant actions *in vivo*. *Psychopharmacol. Berl.* 205 (1), 119–128. doi:10.1007/s00213-009-1521-8
- Abu-Amer, Y. (2013). NF- κ B signaling and bone resorption. *Osteoporos. Int.* 24 (9), 2377–2386. doi:10.1007/s00198-013-2313-x
- Al Shirawi, M. I., Edgar, N. E., and Kennedy, S. H. (2017). Brexpiprazole in the treatment of major depressive disorder. *Clin. Med. Insights Ther.* 9, 1179559X1773180. doi:10.1177/1179559X17731801
- Arai, M., Nagasawa, T., Koshihara, Y., Yamamoto, S., and Togari, A. (2003). Effects of β -adrenergic agonists on bone-resorbing activity in human osteoclast-like cells. *Biochimica Biophysica Acta (BBA) - Mol. Cell Res.* 1640 (2), 137–142. doi:10.1016/s0167-4889(03)00042-9
- Aringhieri, S., Carli, M., Kolachalam, S., Verdesca, V., Cini, E., Rossi, M., et al. (2018). Molecular targets of atypical antipsychotics: From mechanism of action to clinical differences. *Pharmacol. Ther.* 192, 20–41. doi:10.1016/j.pharmthera.2018.06.012
- Arnaiz, J. A., Rodrigues-Silva, C., Mezquida, G., Amoretti, S., Cuesta, M. J., Fraguas, D., et al. (2021). The usefulness of Olanzapine plasma concentrations in monitoring treatment efficacy and metabolic disturbances in first-episode psychosis. *Psychopharmacol. Berl.* 238 (3), 665–676. doi:10.1007/s00213-020-05715-5
- Asano, T., Tanaka, K.-I., Tada, A., Shimamura, H., Tanaka, R., Maruoka, H., et al. (2017). Ameliorative effect of chlorpromazine hydrochloride on visceral hypersensitivity in rats: Possible involvement of 5-HT2a receptor. *Br. J. Pharmacol.* 174 (19), 3370–3381. doi:10.1111/bph.13960
- Australian Institute of Health and Welfare (2022). Mental health-related prescriptions. Available from: <https://www.aihw.gov.au/reports/mental-health-services/mental-health-services-in-australia/report-content/mental-health-related-prescriptions>. (Accessed October 19, 2022).
- Azimi Manavi, B., Stuart, A. L., Pasco, J. A., Hodge, J. M., Samarasinghe, R. M., Weerasinghe, D. K., et al. (2023). Use of antipsychotic medication and its relationship with bone mineral density: A population-based study of men and women. *Front. Psychiatry* 13, 13. doi:10.3389/fpsy.2022.1004366
- Ban, T. A. (2007). Fifty years chlorpromazine: A historical perspective. *Neuropsychiatr. Dis. Treat.* 3 (4), 495–500.
- Battaglini, R., Fu, J., Späte, U., Ersoy, U., Joe, M., Sedaghat, L., et al. (2004). Serotonin regulates osteoclast differentiation through its transporter. *J. Bone Mineral Res.* 19 (9), 1420–1431. doi:10.1359/JBMR.040606
- Baudry, A., Bitard, J., Mouillet-Richard, S., Locker, M., Poliard, A., Launay, J.-M., et al. (2010). Serotonergic 5-HT2B receptor controls tissue-nonspecific alkaline phosphatase activity in osteoblasts via eicosanoids and phosphatidylinositol-specific phospholipase C. *J. Biol. Chem.* 285 (34), 26066–26073. doi:10.1074/jbc.M109.073791
- Becker, D., Liver, O., Mester, R., Rapoport, M., Weizman, A., and Weiss, M. (2003). Risperidone, but not olanzapine, decreases bone mineral density in female premenopausal schizophrenia patients. *J. Clin. Psychiatry* 64 (7), 761–766. doi:10.4088/jcp.v64n0704
- Berger, M., Gray, J. A., and Roth, B. L. (2009). The expanded biology of serotonin. *Annu. Rev. Med.* 60, 355–366. doi:10.1146/annurev.med.60.042307.110802
- Bliziotis, M., Eshleman, A., Burt-Pichat, B., Zhang, X. W., Hashimoto, J., Wiren, K., et al. (2006). Serotonin transporter and receptor expression in osteocytic MLO-Y4 cells. *Bone* 39 (6), 1313–1321. doi:10.1016/j.bone.2006.06.009
- Bliziotis, M. M., Eshleman, A. J., Zhang, X. W., and Wiren, K. M. (2001). Neurotransmitter action in osteoblasts: Expression of a functional system for serotonin receptor activation and reuptake. *Bone* 29 (5), 477–486. doi:10.1016/s8756-3282(01)00593-2
- Boer, M., Castelein, S., Wiersma, D., Schoevers, R., and Knegtering, R. (2015). The facts about sexual (Dys)function in schizophrenia: An overview of clinically relevant findings. *Schizophr. Bull.* 41, 674–686. doi:10.1093/schbul/sbv001
- Bolton, J. M., Morin, S. N., Majumdar, S. R., Sareen, J., Lix, L. M., Johansson, H., et al. (2017). Association of mental disorders and related medication use with risk for major osteoporotic fractures. *JAMA Psychiatry* 74 (6), 641–648. doi:10.1001/jamapsychiatry.2017.0449
- Bonnet, N., Pierroz, D. D., and Ferrari, S. L. (2008). Adrenergic control of bone remodeling and its implications for the treatment of osteoporosis. *J. Musculoskelet. Neuronal Interact.* 8 (2), 94–104.
- Brenner, B., Harney, J. T., Ahmed, B. A., Jeffus, B. C., Unal, R., Mehta, J. L., et al. (2007). Plasma serotonin levels and the platelet serotonin transporter. *J. Neurochem.* 102 (1), 206–215. doi:10.1111/j.1471-4159.2007.04542.x
- Bylund, D. B. (2013). “Adrenergic receptors,” in *Encyclopedia of biological chemistry*. Editors W. J. Lennarz and M. D. Lane Second Edition (Waltham: Academic Press), 57–60.
- Calarge, C. A., Zimmerman, B., Xie, D., Kuperman, S., and Schlechte, J. A. (2010). A cross-sectional evaluation of the effect of risperidone and selective serotonin reuptake inhibitors on bone mineral density in boys. *J. Clin. Psychiatry* 71 (3), 338–347. doi:10.4088/JCP.08m04595gre
- Caplan, A. I. (1991). Mesenchymal stem cells. *J. Orthop. Res.* 9 (5), 641–650. doi:10.1002/jor.1100090504
- Chabbi-Achengli, Y., Coudert Amélie, E., Callebort, J., Geoffroy, V., Côté, F., Collet, C., et al. (2012). Decreased osteoclastogenesis in serotonin-deficient mice. *Proc. Natl. Acad. Sci.* 109 (7), 2567–2572. doi:10.1073/pnas.1117792109
- Chen, H., Tan, X.-N., Hu, S., Liu, R.-Q., Peng, L.-H., Li, Y.-M., et al. (2021). Molecular mechanisms of chondrocyte proliferation and differentiation. *Front. Cell Dev. Biol.* 9. doi:10.3389/fcell.2021.664168
- Cheong, P.-U., Ma, T., Zheng, Y., Ge, X.-Y., Zhang, Y., and Lin, Y. (2018). Dopamine receptor expression on primary osteoblasts and bone marrow mesenchymal stem cells of rats. *Int. J. Clin. Exp. Med.* 11 (3), 1765–1771.
- Chetty, M., and Miller, R. (1991). Effect of storage on the plasma concentration of chlorpromazine and six of its metabolites. *Ther. Drug Monit.* 13 (4), 350–355. doi:10.1097/00007691-199107000-00012
- Ching-Min, K., Wei-Jen, L., Chun-Che, H., Tsuo-Hung, L., Ching-Heng, L., Shun-Ping, W., et al. (2020). Antipsychotic medication in schizophrenic patients is associated with higher risks of developing bone fractures and refractures. *Clin. Psychopharmacol. Neurosci.* 18 (4), 562–570. doi:10.9758/cpn.2020.18.4.562
- Clapham, E., Boden, R., Reutfors, J., Svensson, T., Ramcharran, D., Qiu, H., et al. (2020). Exposure to risperidone versus other antipsychotics and risk of osteoporosis-related fractures: A population-based study. *Acta Psychiatr. Scand.* 141 (1), 74–83. doi:10.1111/acps.13101
- ClinicalTrials.gov (2014). Safety, tolerability, and pharmacokinetics of iloperidone depot in schizophrenic patients ClinicalTrials.gov2014. Available from: <https://clinicaltrials.gov/ct2/show/NCT01348100>.
- Coentre, R., Barrocas, D., and Levy, P. (2009). Low bone mineral density and psychosis: A multifactorial relation. *Eur. Psychiatry* 24 (S1), 1. doi:10.1016/s0924-9338(09)70491-2
- Cohen, J. Y., Dumoulin-Charette, A., Meraabi, N., and Poirier, R. (2019). Serum concentration of paliperidone palmitate administered every 3 weeks. *Psychopharmacol. Bull.* 49 (2), 57–62.
- Collet, C., Schiltz, C., Geoffroy, V., Maroteaux, L., Launay, J. M., and de Vernejoul, M. C. (2008). The serotonin 5-HT2B receptor controls bone mass via osteoblast recruitment and proliferation. *Faseb J.* 22 (2), 418–427. doi:10.1096/fj.07-9209com
- Cookson, J. (2018). Rapid tranquillisation: The science and advice. *BJPsych Adv.* 24, 346–358. doi:10.1192/bja.2018.25
- Correll, C. U., Koblan, K. S., Hopkins, S. C., Li, Y., Heather, D., Goldman, R., et al. (2021). Safety and effectiveness of ulotaront (SEP-363856) in schizophrenia: Results of a 6-month, open-label extension study. *npj Schizophr.* 7 (1), 63. doi:10.1038/s41537-021-00190-z
- Coryell, W., Miller, D. D., and Perry, P. J. (1998). Haloperidol plasma levels and dose optimization. *Am. J. Psychiatry* 155 (1), 48–53. doi:10.1176/ajp.155.1.48
- Costa, J. L., Smith, G., Watson, M., Lin, J.-M., Callon, K., Gamble, G., et al. (2011). The atypical anti-psychotic clozapine decreases bone mass in rats *in vivo*. *Schizophrenia Res.* 126 (1), 291–297. doi:10.1016/j.schres.2010.11.024
- Crews, M. P., and Howes, O. D. (2012). Is antipsychotic treatment linked to low bone mineral density and osteoporosis? A review of the evidence and the clinical implications. *Hum. Psychopharmacol.* 27 (1), 15–23. doi:10.1002/hup.1265
- Cruz Grecco Teixeira, M. B., Martins, G. M., Miranda-Rodrigues, M., De Araujo, I. F., Oliveira, R., Brum, P. C., et al. (2016). Lack of α 2C-adrenoceptor results in contrasting phenotypes of long bones and vertebra and prevents the thyrotoxicosis-induced osteopenia. *PLoS One* 11 (1), e0146795-e. doi:10.1371/journal.pone.0146795
- Dai, S. Q., Yu, L. P., Shi, X., Wu, H., Shao, P., Yin, G. Y., et al. (2014). Serotonin regulates osteoblast proliferation and function *in vitro*. *Braz J. Med. Biol. Res.* 47 (9), 759–765. doi:10.1590/1414-431x20143565
- de Bartolomeis, A., Tomasetti, C., and Iasevoli, F. (2015). Update on the mechanism of action of aripiprazole: Translational insights into antipsychotic strategies beyond dopamine receptor antagonism. *CNS Drugs* 29 (9), 773–799. doi:10.1007/s40263-015-0278-3
- De Hert, M., Detraux, J., van Winkel, R., Yu, W., and Correll, C. U. (2011). Metabolic and cardiovascular adverse effects associated with antipsychotic drugs. *Nat. Rev. Endocrinol.* 8 (2), 114–126. doi:10.1038/nrendo.2011.156
- Del’Guidice, T., Lemasson, M., and Beaulieu, J.-M. (2011). Role of beta-arrestin 2 downstream of dopamine receptors in the basal ganglia. *Front. Neuroanat.* 5, 58. doi:10.3389/fnana.2011.00058
- Dimitri, P., and Rosen, C. (2017). The central nervous system and bone metabolism: An evolving story. *Calcif. Tissue Int.* 100 (5), 476–485. doi:10.1007/s00223-016-0179-6
- Ducy, P., and Karsenty, G. (2010). The two faces of serotonin in bone biology. *J. Cell Biol.* 191 (1), 7–13. doi:10.1083/jcb.201006123
- El Solh, A. (2018). Management of nightmares in patients with posttraumatic stress disorder: Current perspectives. *Nat. Sci. Sleep* 10, 409–420. doi:10.2147/NSS.S166089
- El-Merabhi, R., Löffler, M., Mayer, A., and Sumara, G. (2015). The roles of peripheral serotonin in metabolic homeostasis. *FEBS Lett.* 589 (15), 1728–1734. doi:10.1016/j.febslet.2015.05.054

- Eleftheriou, F., Ahn, J. D., Takeda, S., Starbuck, M., Yang, X., Liu, X., et al. (2005). Leptin regulation of bone resorption by the sympathetic nervous system and CART. *Nature* 434 (7032), 514–520. doi:10.1038/nature03398
- Elenkov, I. J., Wilder, R., Chrousos, G., and Vizi, E. (2001). The sympathetic nerve—an integrative interface between two supersystems: The brain and the immune system. *Pharmacol. Rev.* 52, 595–638.
- Florencio-Silva, R., Sasso, G. RdS., Sasso-Cerri, E., Simões, M. J., and Cerri, P. S. (2015). Biology of bone tissue: Structure, function, and factors that influence bone cells. *Biomed. Res. Int.* 2015, 421746. doi:10.1155/2015/421746
- Foley, P., Gerlach, M., Double, K., and Riederer, P. (2004). Dopamine receptor agonists in the therapy of Parkinson's disease. *Acta Neuroveg.* 111, 1375–1446. doi:10.1007/s00702-003-0059-x
- Forns, J., Layton, J. B., Bartsch, J., Turner, M. E., Dempsey, C., Anthony, M., et al. (2021). Increased risk of falls and fractures in patients with psychosis and Parkinson disease. *PLoS One* 16 (1), e0246121. doi:10.1371/journal.pone.0246121
- Frankel, J. S., and Schwartz, T. L. (2017). Brexpiprazole and cariprazine: Distinguishing two new atypical antipsychotics from the original dopamine stabilizer aripiprazole. *Ther. Adv. Psychopharmacol.* 7 (1), 29–41. doi:10.1177/2045125316672136
- Fraser, L.-A., Liu, K., Naylor, K. L., Hwang, Y. J., Dixon, S. N., Shariff, S. Z., et al. (2015). Falls and fractures with atypical antipsychotic medication use: A population-based cohort study. *JAMA Intern. Med.* 175 (3), 450–452. doi:10.1001/jamainternmed.2014.6930
- Gaskill, P. J., Carvallo, L., Eugenin, E. A., and Berman, J. W. (2012). Characterization and function of the human macrophage dopaminergic system: Implications for CNS disease and drug abuse. *J. Neuroinflammation* 9 (1), 203. doi:10.1186/1742-2094-9-203
- Gesty-Palmer, D., Flannery, P., Yuan, L., Corsino, L., Spurney, R., Lefkowitz, R. J., et al. (2009). A beta-arrestin-biased agonist of the parathyroid hormone receptor (PTH1R) promotes bone formation independent of G protein activation. *Sci. Transl. Med.* 1 (1), 1ra1. doi:10.1126/scitranslmed.3000071
- Graham, R. M. (1990). Adrenergic receptors: Structure and function. *Cleveland Clin. J. Med.* 57 (5), 481–491. doi:10.3949/cjcm.57.5.481
- Gustafsson, B. I., Thommesen, L., Stunes, A. K., Tommeras, K., Westbroek, I., Waldum, H. L., et al. (2006). Serotonin and fluoxetine modulate bone cell function *in vitro*. *J. Cell Biochem.* 98 (1), 139–151. doi:10.1002/jcb.20734
- Gustafsson, B. I., Westbroek, I., Waarsing, J. H., Waldum, H., Solligård, E., Brunsvik, A., et al. (2006). Long-term serotonin administration leads to higher bone mineral density, affects bone architecture, and leads to higher femoral bone stiffness in rats. *J. Cell Biochem.* 97 (6), 1283–1291. doi:10.1002/jcb.20733
- Haddad, P. M., and Correll, C. U. (2018). The acute efficacy of antipsychotics in schizophrenia: A review of recent meta-analyses. *Ther. Adv. Psychopharmacol.* 8 (11), 303–318. doi:10.1177/2045125318781475
- Hálfánarson, Ó., Zoëga, H., Aagaard, L., Bernardo, M., Brandt, L., Fusté, A. C., et al. (2017). International trends in antipsychotic use: A study in 16 countries, 2005–2014. *Eur. Neuropsychopharmacol.* 27 (10), 1064–1076. doi:10.1016/j.euroneuro.2017.07.001
- Hamajima, K., Hamamura, K., Chen, A., Yokota, H., Mori, H., Yo, S., et al. (2018). Suppression of osteoclastogenesis via α 2-adrenergic receptors. *Biomed. Rep.* 8 (5), 407–416. doi:10.3892/br.2018.1075
- Hanami, K., Nakano, K., Saito, K., Okada, Y., Yamaoka, K., Kubo, S., et al. (2013). Dopamine D2-like receptor signaling suppresses human osteoclastogenesis. *Bone* 56 (1), 1–8. doi:10.1016/j.bone.2013.04.019
- Handa, K., Kiyohara, S., Yamakawa, T., Ishikawa, K., Hosonuma, M., Sakai, N., et al. (2019). Bone loss caused by dopaminergic degeneration and levodopa treatment in Parkinson's disease model mice. *Sci. Rep.* 9 (1), 13768. doi:10.1038/s41598-019-50336-4
- Handley, S. A., Bowskill, S. V. J., Patel, M. X., and Flanagan, R. J. (2013). Plasma quetiapine in relation to prescribed dose and other factors: Data from a therapeutic drug monitoring service, 2000–2011. *Ther. Adv. Psychopharmacol.* 3 (3), 129–137. doi:10.1177/2045125312470677
- Hattori, N., Hasegawa, K., and Sakamoto, T. (2012). Pharmacokinetics and effect of food after oral administration of prolonged-release tablets of ropinirole hydrochloride in Japanese patients with Parkinson's disease. *J. Clin. Pharm. Ther.* 37 (5), 571–577. doi:10.1111/j.1365-2710.2012.01336.x
- Hill, E. L., and Elde, R. (1991). Distribution of CGRP-VP-D beta H-SP-and NPY-immunoreactive nerves in the periosteum of the rat. *Cell Tissue Res.* 264 (3), 469–480. doi:10.1007/BF00319037
- Hioki, T., Kuroyanagi, G., Matsushima-Nishiwaki, R., Kozawa, O., and Tokuda, H. (2022). Oncostatin M attenuates tumor necrosis factor- α -induced synthesis of macrophage-colony stimulating factor via suppression of Akt in osteoblasts. *Connect. Tissue Res.*, 1–9.
- Hodge, J. M., Wang, Y., Berk, M., Collier, F. M., Fernandes, T. J., Constable, M. J., et al. (2013). Selective serotonin reuptake inhibitors inhibit human osteoclast and osteoblast formation and function. *Biol. Psychiatry* 74 (1), 32–39. doi:10.1016/j.biopsych.2012.11.003
- Hornykiewicz, O. (2017). L-DOPA. *J. Park. Dis.* 7 (1), S3–S10. doi:10.3233/jpd-179004
- Houseknecht, K. L., Bouchard, C. C., and Black, C. A. (2017). Elucidating the mechanism(s) underlying antipsychotic and antidepressant-mediated fractures. *J. Ment. Health Clin. Psychol.* 1 (1), 9–13. doi:10.29245/2578-2959/2018/1.1106
- Howes, O. D., Egerton, A., Allan, V., McGuire, P., Stokes, P., and Kapur, S. (2009). Mechanisms underlying psychosis and antipsychotic treatment response in schizophrenia: Insights from PET and SPECT imaging. *Curr. Pharm. Des.* 15 (22), 2550–2559. doi:10.2174/138161209788957528
- Huang, H. H., Brennan, T. C., Muir, M. M., and Mason, R. S. (2009). Functional α 1- and β 2-adrenergic receptors in human osteoblasts. *J. Cell. Physiology* 220 (1), 267–275. doi:10.1002/jcp.21761
- Ishibashi, T., Horisawa, T., Tokuda, K., Ishiyama, T., Ogasa, M., Tagashira, R., et al. (2010). Pharmacological profile of lurasidone, a novel antipsychotic agent with potent 5-hydroxytryptamine 7 (5-HT7) and 5-HT1A receptor activity. *J. Pharmacol. Exp. Ther.* 334 (1), 171–181. doi:10.1124/jpet.110.167346
- Jiao, K., Niu, L.-N., Li, Q.-H., Ren, G.-T., Zhao, C.-M., Liu, Y.-D., et al. (2015). β 2-adrenergic signal transduction plays a detrimental role in subchondral bone loss of temporomandibular joint in osteoarthritis. *Sci. Rep.* 5 (1), 12593. doi:10.1038/srep12593
- Jörg, M., Scammells, P. J., Capuano, B., Kaczor, A. A., Poso, A., Mak, F. S., et al. (2014). Investigation of novel ropinirole analogues: Synthesis, pharmacological evaluation and computational analysis of dopamine D2 receptor functionalized congeners and homobivalent ligands. *MedChemComm* 5 (7), 891–898. doi:10.1039/c4md00066h
- Jung, D.-U., Kelly, D. L., Oh, M.-K., Kong, B.-G., Kang, J.-W., Lee, S.-J., et al. (2011). Bone mineral density and osteoporosis risk in older patients with schizophrenia. *J. Clin. Psychopharmacol.* 31 (4), 406–410. doi:10.1097/JCP.0b013e318221b123
- Kajimura, D., Hinoi, E., Ferron, M., Kode, A., Riley, K. J., Zhou, B., et al. (2011). Genetic determination of the cellular basis of the sympathetic regulation of bone mass accrual. *J. Exp. Med.* 208 (4), 841–851. doi:10.1084/jem.20102608
- Kanova, M., and Kohout, P. (2021). Serotonin-its synthesis and roles in the healthy and the critically ill. *Int. J. Mol. Sci.* 22 (9), 4837. doi:10.3390/ijms22094837
- Kawamura, H., Arai, M., and Togari, A. (2011). Inhibitory effect of chlorpromazine on RANKL-induced osteoclastogenesis in mouse bone marrow cells. *J. Pharmacol. Sci.* 117 (1), 54–62. doi:10.1254/jphs.11006fp
- Kellenberger, S., Muller, K., Richener, H., and Bilbe, G. (1998). Formoterol and isoproterenol induce c-fos gene expression in osteoblast-like cells by activating β 2-adrenergic receptors. *Bone* 22 (5), 471–478. doi:10.1016/s8756-3282(98)00026-x
- Kenkre, J. S., and Bassett, J. (2018). The bone remodelling cycle. *Ann. Clin. Biochem.* 55 (3), 308–327. doi:10.1177/0004563218759371
- Khosla, S., Drake, M. T., Volkman, T. L., Thicke, B. S., Achenbach, S. J., Atkinson, E. J., et al. (2018). Sympathetic β 1-adrenergic signaling contributes to regulation of human bone metabolism. *J. Clin. Investigation* 128 (11), 4832–4842. doi:10.1172/JCI122151
- Kim, J. M., Yang, Y. S., Park, K. H., Oh, H., Greenblatt, M. B., and Shim, J. H. (2019). The ERK MAPK pathway is essential for skeletal development and homeostasis. *Int. J. Mol. Sci.* 20 (8), 1803. doi:10.3390/ijms20081803
- Kishimoto, T., Watanabe, K., Shimada, N., Makita, K., Yagi, G., and Kashima, H. (2008). Antipsychotic-induced hyperprolactinemia inhibits the hypothalamo-pituitary-gonadal axis and reduces bone mineral density in male patients with schizophrenia. *J. Clin. Psychiatry* 69 (3), 385–391. doi:10.4088/jcp.v69n0307
- Kiss, B., Horváth, A., Némethy, Z., Schmidt, E., Laszlovsky, I., Bugovics, G., et al. (2010). Cariprazine (RGH-188), a dopamine D(3) receptor-preferring, D(3)/D(2) dopamine receptor antagonist-partial agonist antipsychotic candidate: *In vitro* and neurochemical profile. *J. Pharmacol. Exp. Ther.* 333 (1), 328–340. doi:10.1124/jpet.109.160432
- Kiss, B., Krámos, B., and Laszlovsky, I. (2022). Potential mechanisms for why not all antipsychotics are able to occupy dopamine D3 receptors in the brain *in vivo*. *Front. Psychiatry* 13, 785592. doi:10.3389/fpsy.2022.785592
- Kiss, B., Némethy, Z., Fazekas, K., Kurkó, D., Gyertyán, I., Sághy, K., et al. (2019). Preclinical pharmacodynamic and pharmacokinetic characterization of the major metabolites of cariprazine. *Drug Des. Devel Ther.* 13, 3229–3248. doi:10.2147/DDDT.S188760
- Kode, A., Mosialou, I., Silva, B. C., Rached, M. T., Zhou, B., Wang, J., et al. (2012). FOXO1 orchestrates the bone-suppressing function of gut-derived serotonin. *J. Clin. Invest.* 122 (10), 3490–3503. doi:10.1172/JCI64906
- Kondo, H., Takeuchi, S., and Togari, A. (2013). β -Adrenergic signaling stimulates osteoclastogenesis via reactive oxygen species. *Am. J. Physiol. Endocrinol. Metab.* 304 (5), E507–E515. doi:10.1152/ajpendo.00191.2012
- Kunimatsu, T., Kimura, J., Funabashi, H., Inoue, T., and Seki, T. (2010). The antipsychotics haloperidol and chlorpromazine increase bone metabolism and induce osteopenia in female rats. *Regul. Toxicol. Pharmacol.* 58 (3), 360–368. doi:10.1016/j.yrtph.2010.08.001
- Laborit, H., Huguenard, P., and Alluaume, R. (1952). A new vegetative stabilizer; 4560 R.P. *Presse Med.* 60 (10), 206–208.
- Lahdelma, L., Oja, S., Korhonen, M., and Andersson, L. C. (2010). Clozapine is cytotoxic to primary cultures of human bone marrow mesenchymal stromal cells. *J. Clin. Psychopharmacol.* 30 (4), 461–463. doi:10.1097/JCP.0b013e3181e6a082

- Lally, J. (2020). *Bone health in psychotic disorders, and risk factors for decreased bone health in established and early psychosis*. Royal College of Surgeons in Ireland.
- Lally, J., and MacCabe, J. H. (2015). Antipsychotic medication in schizophrenia: A review. *Br. Med. Bull.* 114 (1), 169–179. doi:10.1093/bmb/ldv017
- Lee, D. J., Tseng, H. C., Wong, S. W., Wang, Z., Deng, M., and Ko, C.-C. (2015). Dopaminergic effects on *in vitro* osteogenesis. *Bone Res.* 3 (1), 15020. doi:10.1038/boneres.2015.20
- Lee, J. Y., Yang, J.-Y., and Kim, S. W. (2021). Bone lining cells could be sources of bone marrow adipocytes. *Front. Endocrinol.* 12, 766254. doi:10.3389/fendo.2021.766254
- Lencsova, L., Szadvari, I., Babula, P., Kubickova, J., Chovancova, B., Lopusna, K., et al. (2017). Disruption of dopamine D1/D2 receptor complex is involved in the function of haloperidol in cardiac H9c2 cells. *Life Sci.* 191, 186–194. doi:10.1016/j.lfs.2017.10.026
- Lesclous, P., Guez, D., Llorens, A., and Saffar, J. L. (2001). Time-course of mast cell accumulation in rat bone marrow after ovariectomy. *Calcif. Tissue Int.* 68 (5), 297–303. doi:10.1007/BF02390837
- Li, P., Snyder, G. L., and Vanover, K. E. (2016). Dopamine targeting drugs for the treatment of schizophrenia: Past, present and future. *Curr. Top. Med. Chem.* 16 (29), 3385–3403. doi:10.2174/1568026616666160608084834
- Li, P., Wang, Y., Liu, X., Zhou, Z., Wang, J., Zhou, H., et al. (2019). Atypical antipsychotics induce human osteoblasts apoptosis via Wnt/ β -catenin signaling. *BMC Pharmacol. Toxicol.* 20 (1), 10. doi:10.1186/s40360-019-0287-9
- Lieberman, J. A., 3rd. (2004). Metabolic changes associated with antipsychotic use. *Prim. Care Companion J. Clin. Psychiatry* 6 (2), 8–13.
- Ma, Y., Nyman, J. S., Tao, H., Moss, H. H., Yang, X., and Elefteriou, F. (2011). β 2-Adrenergic receptor signaling in osteoblasts contributes to the catabolic effect of glucocorticoids on bone. *Endocrinology* 152 (4), 1412–1422. doi:10.1210/en.2010-0881
- Maeda, K., Sugino, H., Akazawa, H., Amada, N., Shimada, J., Futamura, T., et al. (2014). Brexpiprazole I: *In vitro* and *in vivo* characterization of a novel serotonin-dopamine activity modulator. *J. Pharmacol. Exp. Ther.* 350 (3), 589–604. doi:10.1124/jpet.114.213793
- Mahapatra, J., Quraishi, S. N., David, A., Sampson, S., and Adams, C. E. (2014). Flupenthixol decanoate (depot) for schizophrenia or other similar psychotic disorders. *Cochrane Database Syst. Rev.* 2014 (6), Cd001470. doi:10.1002/14651858.CD001470.pub2
- Mailman, R. B., and Murthy, V. (2010). Third generation antipsychotic drugs: Partial agonism or receptor functional selectivity? *Curr. Pharm. Des.* 16 (5), 488–501. doi:10.2174/138161210790361461
- Maramai, S., Gemma, S., Brogi, S., Campiani, G., Butini, S., Stark, H., et al. (2016). Dopamine D3 receptor antagonists as potential therapeutics for the treatment of neurological diseases. *Front. Neurosci.* 10, 451. doi:10.3389/fnins.2016.00451
- Marino, J., and Caballero, J. (2010). Iloperidone for the treatment of schizophrenia. *Ann. Pharmacother.* 44, 863–870. doi:10.1345/aph.1M603
- Martel, J. C., and Gatti McArthur, S. (2020). Dopamine receptor subtypes, physiology and pharmacology: New ligands and concepts in schizophrenia. *Front. Pharmacol.* 11, 1003. doi:10.3389/fphar.2020.01003
- Matt, S. M., and Gaskill, P. J. (2020). Where is dopamine and how do immune cells see it?: Dopamine-mediated immune cell function in health and disease. *J. Neuroimmune Pharmacol.* 15 (1), 114–164. doi:10.1007/s11481-019-09851-4
- Mauri, M. C., Paletta, S., Maffini, M., Colasanti, A., Dragogna, F., Di Pace, C., et al. (2014). Clinical pharmacology of atypical antipsychotics: An update. *EXCLI J.* 13, 1163–1191.
- May, M., Beauchemin, M., Vary, C., Barlow, D., and Houseknecht, K. L. (2019). The antipsychotic medication, risperidone, causes global immunosuppression in healthy mice. *PLoS one* 14 (6), e0218937. doi:10.1371/journal.pone.0218937
- McCorry, J. D., and Roth, B. L. (2015). Structure and function of serotonin G protein-coupled receptors. *Pharmacol. Ther.* 150, 129–142. doi:10.1016/j.pharmthera.2015.01.009
- McCutcheon, R., Beck, K., Jauhar, S., and Howes, O. D. (2018). Defining the locus of dopaminergic dysfunction in schizophrenia: A meta-analysis and test of the mesolimbic hypothesis. *Schizophr. Bull.* 44 (6), 1301–1311. doi:10.1093/schbul/sbx180
- McCutcheon, R. A., Abi-Dargham, A., and Howes, O. D. (2019). Schizophrenia, dopamine and the striatum: From biology to symptoms. *Trends Neurosci.* 42 (3), 205–220. doi:10.1016/j.tins.2018.12.004
- Meltzer, H. Y. (1994). An overview of the mechanism of action of clozapine. *J. Clin. Psychiatry* 55, 47–52.
- Meltzer, H. Y., and Massey, B. W. (2011). The role of serotonin receptors in the action of atypical antipsychotic drugs. *Curr. Opin. Pharmacol.* 11 (1), 59–67. doi:10.1016/j.coph.2011.02.007
- Méndez-Ferrer, S., Michurina, T. V., Ferraro, F., Mazloom, A. R., MacArthur, B. D., Lira, S. A., et al. (2010). Mesenchymal and hematopoietic stem cells form a unique bone marrow niche. *Nature* 466 (7308), 829–834. doi:10.1038/nature09262
- Metzger, C. E., and Narayanan, S. A. (2019). The role of osteocytes in inflammatory bone loss. *Front. Endocrinol.* 10, 285. doi:10.3389/fendo.2019.00285
- Midha, K. K., Korchinski, E. D., Verbeeck, R. K., Roscoe, R. M., Hawes, E. M., Cooper, J. K., et al. (1983). Kinetics of oral trifluoperazine disposition in man. *Br. J. Clin. Pharmacol.* 15 (3), 380–382. doi:10.1111/j.1365-2125.1983.tb01515.x
- Miron, R. J., and Bosshardt, D. D. (2016). OsteoMacs: Key players around bone biomaterials. *Biomaterials* 82, 1–19. doi:10.1016/j.biomaterials.2015.12.017
- Mohamad, S. F., Gunawan, A., Blosser, R., Childress, P., Aguilar-Perez, A., Ghosh, J., et al. (2021). Neonatal osteomacs and bone marrow macrophages differ in phenotypic marker expression and function. *J. Bone Mineral Res.* 36 (8), 1580–1593. doi:10.1002/jbmr.4314
- Möller, H. J. (2003). Amisulpride: Limbic specificity and the mechanism of antipsychotic atypicality. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 27 (7), 1101–1111. doi:10.1016/j.pnpbp.2003.09.006
- Moriya, S., Hayata, T., Notomi, T., Aryal, S., Nakamaoto, T., Izu, Y., et al. (2015). PTH regulates β 2-adrenergic receptor expression in osteoblast-like mc3t3-E1 cells. *J. Cell. Biochem.* 116 (1), 142–148. doi:10.1002/jcb.24953
- Motyl, K. J., Beauchemin, M., Barlow, D., Le, P. T., Nagano, K., Treyball, A., et al. (2017). A novel role for dopamine signaling in the pathogenesis of bone loss from the atypical antipsychotic drug risperidone in female mice. *Bone* 103, 168–176. doi:10.1016/j.bone.2017.07.008
- Motyl, K. J., Dick-de-Paula, I., Maloney, A. E., Lotinun, S., Bornstein, S., de Paula, F. J. A., et al. (2012). Trabecular bone loss after administration of the second-generation antipsychotic risperidone is independent of weight gain. *Bone* 50 (2), 490–498. doi:10.1016/j.bone.2011.08.005
- Nagasawa, S., Yamaguchi, R., Saka, K., Torimitsu, S., Chiba, F., Yajima, D., et al. (2017). Risperidone involved in a fatal case: Blood and urinary concentrations. *Forensic Toxicol.* 40 (1), 173–179. doi:10.1007/s11419-021-00593-8
- Nakashioya, H., Nakano, K., Watanabe, N., Miyasaka, N., Matsushita, S., and Kohsaka, H. (2011). Therapeutic effect of D1-like dopamine receptor antagonist on collagen-induced arthritis of mice. *Mod. Rheumatol.* 21 (3), 260–266. doi:10.1007/s10165-010-0387-2
- Neve, K. A., Seamans, J. K., and Trantham-Davidson, H. (2004). Dopamine receptor signaling. *J. Recept. Signal Transduct.* 24 (3), 165–205. doi:10.1081/rrs-200029981
- Nichols, D. E., and Nichols, C. D. (2008). Serotonin receptors. *Chem. Rev.* 108 (5), 1614–1641. doi:10.1021/cr078224o
- Nishiura, T., and Abe, K. (2007). Alpha1-adrenergic receptor stimulation induces the expression of receptor activator of nuclear factor kappaB ligand gene via protein kinase C and extracellular signal-regulated kinase pathways in MC3T3-E1 osteoblast-like cells. *Archives Oral Biol.* 52 (8), 778–785. doi:10.1016/j.archoralbio.2007.01.005
- Oderda, L. H., Young, J. R., Asche, C. V., and Pepper, G. A. (2012). Psychotropic-related hip fractures: Meta-analysis of first-generation and second-generation antidepressant and antipsychotic drugs. *Ann. Pharmacother.* 46 (7–8), 917–928. doi:10.1345/aph.1Q589
- Oh-ie, K., Miyazaki, T., Koyama, I., Hokari, S., and Komoda, T. (2002). Altered bone turnover in chlorpromazine-challenged rats and its effect on 1alpha-hydroxyvitamin D3 administration *in vivo*. *J. Bone Mineral Metabolism* 20 (1), 21–27. doi:10.1007/s774-002-8442-7
- Omérov, M., Wistedt, B., Bolvig-Hansen, L., and Larsen, N. E. (1989). The relationship between perphenazine plasma levels and clinical response in acute schizophrenia. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 13 (1–2), 159–166. doi:10.1016/0278-5846(89)90013-4
- Papola, D., Ostuzzi, G., Thabane, L., Guyatt, G., and Barbui, C. (2018). Antipsychotic drug exposure and risk of fracture: A systematic review and meta-analysis of observational studies. *Int. Clin. Psychopharmacol.* 33 (4), 181–196. doi:10.1097/YIC.0000000000000221
- Park, K.-R., Kim, E.-C., Hong, J. T., and Yun, H.-M. (2018). Dysregulation of 5-hydroxytryptamine 6 receptor accelerates maturation of bone-resorbing osteoclasts and induces bone loss. *Theranostics* 8 (11), 3087–3098. doi:10.7150/thno.24426
- Paschou, S. A., Mentzelopoulos, P., and Lambrinouadaki, I. (2019). Antipsychotic therapies and bone health. *Case Rep. Womens Health* 25, e00160–e. doi:10.1016/j.crw.2019.e00160
- Pasco, J. A., Henry, M. J., Sanders, K. M., Kotowicz, M. A., Seeman, E., Nicholson, G. C., et al. (2004). Beta-adrenergic blockers reduce the risk of fracture partly by increasing bone mineral density: Geelong Osteoporosis Study. *J. Bone Mineral Res.* 19 (1), 19–24. doi:10.1359/JBMR.0301214
- Patel, K. R., Cherian, J., Gohil, K., and Atkinson, D. (2014). Schizophrenia: Overview and treatment options. *P T* 39 (9), 638–645.
- Perez, D. M. (2020). α 1-Adrenergic receptors in neurotransmission, synaptic plasticity, and cognition. *Front. Pharmacol.* 11, 581098. doi:10.3389/fphar.2020.581098
- Pillinger, T., McCutcheon, R. A., Vano, L., Mizuno, Y., Arumuham, A., Hindley, G., et al. (2020). Comparative effects of 18 antipsychotics on metabolic function in patients with schizophrenia, predictors of metabolic dysregulation, and association with psychopathology: A systematic review and network meta-analysis. *Lancet Psychiatry* 7 (1), 64–77. doi:10.1016/S2215-0366(19)30416-X

- Pittenger, M. F., Mackay, A. M., Beck, S. C., Jaiswal, R. K., Douglas, R., Mosca, J. D., et al. (1999). Multilineage potential of adult human mesenchymal stem cells. *Science* 284 (5411), 143–147. doi:10.1126/science.284.5411.143
- Pożarowska, K., Rusinek, A., Rudziński, G., Soroka, E., and Masiak, J. (2021). New drugs in psychiatry - cariprazine, lurasidone, esketamine. *Curr. Problems Psychiatry* 22 (2), 111–124. doi:10.2478/cpp-2021-0010
- Prieto, E., Micó, J. A., Meana, J. J., and Majadas, S. (2010). Neurobiological bases of quetiapine antidepressant effect in the bipolar disorder. *Actas Esp. Psiquiatr.* 38 (1), 22–32.
- Ramachandiraiah, C. T., Subramaniam, N., and Tancer, M. (2009). The story of antipsychotics: Past and present. *Indian J. Psychiatry* 51 (4), 324–326. doi:10.4103/0019-5545.58304
- Ramaswamy, G., Kim, H., Zhang, D., Lounev, V., Wu, J. Y., Choi, Y., et al. (2017). Gsa controls cortical bone quality by regulating osteoclast differentiation via cAMP/PKA and β -catenin pathways. *Sci. Rep.* 7 (1), 45140. doi:10.1038/srep45140
- Rampino, A., Marakhovskaia, A., Soares-Silva, T., Torretta, S., Veneziani, F., and Beaulieu, J. M. (2019). Antipsychotic drug responsiveness and dopamine receptor signaling: old players and new prospects. *Front. Psychiatry* 9, 702. doi:10.3389/fpsy.2018.00702
- Richtand, N., Welge, J., Logue, A., Keck, P., Strakowski, S., and McNamara, R. (2007). Dopamine and serotonin receptor binding and antipsychotic efficacy. *Neuropsychopharmacology* 32:1715–1726. doi:10.1038/sj.npp.1301305
- Rigler, S. K., Shireman, T. L., Cook-Wiens, G. J., Ellerbeck, E. F., Whittle, J. C., Mehr, D. R., et al. (2013). Fracture risk in nursing home residents initiating antipsychotic medications. *J. Am. Geriatr. Soc.* 61 (5), 715–722. doi:10.1111/jgs.12216
- Rosenbloom, A. L. (2010). Hyperprolactinemia with antipsychotic drugs in children and adolescents. *Int. J. Pediatr. Endocrinol.* 2010, 159402. doi:10.1155/2010/159402
- Sacchetti, B., Funari, A., Michienzi, S., Di Cesare, S., Piersanti, S., Saggio, I., et al. (2007). Self-renewing osteoprogenitors in bone marrow sinusoids can organize a hematopoietic microenvironment. *Cell* 131 (2), 324–336. doi:10.1016/j.cell.2007.08.025
- Saller, C. F., and Salama, A. I. (1993). Seroquel: Biochemical profile of a potential atypical antipsychotic. *Psychopharmacol. Berl.* 112 (2-3), 285–292. doi:10.1007/BF02244923
- Sato, T., Arai, M., Goto, S., and Togari, A. (2010). Effects of propranolol on bone metabolism in spontaneously hypertensive rats. *J. Pharmacol. Exp. Ther.* 334 (1), 99–105. doi:10.1124/jpet.110.167643
- Schreiber, S., and Pick, C. G. (2021). The opioid interactions of the antipsychotic medications risperidone and amisulpride in mice and their potential use in the treatment of other non-psychotic medical conditions. *Cell. Mol. Neurobiol.* 41 (5), 1077–1084. doi:10.1007/s10571-020-01001-2
- Sekhar, G. N., Fleckney, A. L., Boyanova, S. T., Rupawala, H., Lo, R., Wang, H., et al. (2019). Region-specific blood–brain barrier transporter changes leads to increased sensitivity to amisulpride in Alzheimer's disease. *Fluids Barriers CNS* 16 (1), 38. doi:10.1186/s12987-019-0158-1
- Shapiro, D. A., Renock, S., Arrington, E., Chiodo, L. A., Liu, L. X., Sibley, D. R., et al. (2003). Aripiprazole, a novel atypical antipsychotic drug with a unique and robust pharmacology. *Neuropsychopharmacology* 28 (8), 1400–1411. doi:10.1038/sj.npp.1300203
- Shen, S. P., Liu, Y., Qiu, H., Tsai, K. Y., Wu, H. C., Liang, W. M., et al. (2019). The risk of bone fracture after long-term risperidone exposure is not increased compared to other atypical antipsychotics: A retrospective cohort study. *PLoS One* 14 (9), e0221948. doi:10.1371/journal.pone.0221948
- Shirley, M., and Perry, C. M. (2014). Aripiprazole (abilify MAINTENA®): A review of its use as maintenance treatment for adult patients with schizophrenia. *Drugs* 74, 1097–1110. doi:10.1007/s40265-014-0231-7
- Siafis, S., Tzachanis, D., Samara, M., and Papazisis, G. (2018). Antipsychotic drugs: From receptor-binding profiles to metabolic side effects. *Curr. Neuropharmacol.* 16 (8), 1210–1223. doi:10.2174/1570159X15666170630163616
- Siddappa, R., Mulder, W., Steeghs, L., van de Klundert, C., Fernandes, H., Liu, J., et al. (2009). cAMP/PKA signaling inhibits osteogenic differentiation and bone formation in rodent models. *Tissue Eng. Part A* 15 (8), 2135–2143. doi:10.1089/ten.tea.2008.0512
- Stahl, S. M. (2018). Beyond the dopamine hypothesis of schizophrenia to three neural networks of psychosis: Dopamine, serotonin, and glutamate. *CNS Spectrums* 23 (3), 187–191. doi:10.1017/S1092852918001013
- Strange, P. G. (2008). Antipsychotic drug action: Antagonism, inverse agonism or partial agonism. *Trends Pharmacol. Sci.* 29 (6), 314–321. doi:10.1016/j.tips.2008.03.009
- Stubbs, B., Gaughran, F., Mitchell, A. J., De Hert, M., Farmer, R., Soundy, A., et al. (2015). Schizophrenia and the risk of fractures: A systematic review and comparative meta-analysis. *General Hosp. Psychiatry* 37 (2), 126–133. doi:10.1016/j.genhosppsych.2015.01.004
- Suga, S., Goto, S., and Togari, A. (2010). Demonstration of direct neurite–osteoclastic cell communication *in vitro* via the adrenergic receptor. *J. Pharmacol. Sci.* 112 (2), 184–191. doi:10.1254/jphs.09283fp
- Takeda, S., Eleferiou, F., Levasseur, R., Liu, X., Zhao, L., Parker, K. L., et al. (2002). Leptin regulates bone formation via the sympathetic nervous system. *Cell* 111 (3), 305–317. doi:10.1016/s0092-8674(02)01049-8
- Togari, A. (2002). Adrenergic regulation of bone metabolism: Possible involvement of sympathetic innervation of osteoblastic and osteoclastic cells. *Microsc. Res. Tech.* 58 (2), 77–84. doi:10.1002/jemt.10121
- Togari, A., Arai, M., Mizutani, S., Mizutani, S., Koshihara, Y., and Nagatsu, T. (1997). Expression of mRNAs for neuropeptide receptors and β -adrenergic receptors in human osteoblasts and human osteogenic sarcoma cells. *Neurosci. Lett.* 233 (2), 125–128. doi:10.1016/s0304-3940(97)00649-6
- Tollefson, G. D., and Taylor, C. C. (2000). Olanzapine: Preclinical and clinical profiles of a novel antipsychotic agent. *CNS Drug Rev.* 6 (4), 303–363. doi:10.1111/j.1527-3458.2000.tb00155.x
- Tsai, K.-Y., Lee, C.-C., Chou, Y.-M., Shen, S.-P., Su, C.-Y., Wu, H.-C., et al. (2014). The risks of major osteoporotic fractures in patients with schizophrenia: A population-based 10-year follow-up study. *Schizophrenia Res.* 159 (2), 322–328. doi:10.1016/j.schres.2014.09.032
- Tseng, P. T., Chen, Y. W., Yeh, P. Y., Tu, K. Y., Cheng, Y. S., and Wu, C. K. (2015). Bone mineral density in schizophrenia: An update of current meta-analysis and literature review under guideline of PRISMA. *Med. Baltim.* 94 (47), e1967. doi:10.1097/MD.0000000000001967
- van Gastel, J., Hendrickx, J. O., Leysen, H., Santos-Otte, P., Luttrell, L. M., Martin, B., et al. (2018). β -Arrestin based receptor signaling paradigms: Potential therapeutic targets for complex age-related disorders. *Front. Pharmacol.* 9, 1369. doi:10.3389/fphar.2018.01369
- Van Putten, T., Marder, S. R., Wirshing, W. C., Aravagiri, M., and Chabert, N. (1991). Neuroleptic plasma levels. *Schizophr. Bull.* 17 (2), 197–216. doi:10.1093/schbul/17.2.197
- Vasilu, O. (2022). Third-generation antipsychotics in patients with schizophrenia and non-responsivity or intolerance to clozapine regimen: What is the evidence? *Front. Psychiatry* 13, 1069432. doi:10.3389/fpsy.2022.1069432
- Walker, E. C., McGregor, N. E., Poulton, I. J., Solano, M., Pompolo, S., Fernandes, T. J., et al. (2010). Oncostatin M promotes bone formation independently of resorption when signaling through leukemia inhibitory factor receptor in mice. *J. Clin. Invest.* 120 (2), 582–592. doi:10.1172/JCI40568
- Wang, C.-X., Ge, X.-Y., Wang, M.-Y., Ma, T., Zhang, Y., and Lin, Y. (2020). Dopamine D1 receptor-mediated activation of the ERK signaling pathway is involved in the osteogenic differentiation of bone mesenchymal stem cells. *Stem Cell Res. Ther.* 11 (1), 12. doi:10.1186/s13287-019-1529-x
- Wang, H., Xu, J., Lazarovici, P., Quirion, R., and Zheng, W. (2018). cAMP response element-binding protein (CREB): A possible signaling molecule link in the pathophysiology of schizophrenia. *Front. Mol. Neurosci.* 11, 255. doi:10.3389/fnmol.2018.00255
- Wang, J., Jiang, F., Yang, Y., Zhang, Y., Liu, Z., Qin, X., et al. (2021). Description of three new species of the leafhopper genus *Idioscopus* baker, (Hemiptera: Cicadellidae: Eurymelinae) from yunnan, China. *BMC Psychiatry* 21 (1), 375–381. doi:10.1186/s12932-021-00923-0
- Wang, L., Han, L., Xue, P., Hu, X., Wong, S.-W., Deng, M., et al. (2021). Dopamine suppresses osteoclast differentiation via cAMP/PKA/CREB pathway. *Cell Signal* 78, 109847. doi:10.1016/j.celsig.2020.109847
- Watanabe, Y., Yamada, S., Otsubo, T., and Kikuchi, T. (2020). Brexpiprazole for the treatment of schizophrenia in adults: An overview of its clinical efficacy and safety and a psychiatrist's perspective. *Drug Des. Devel. Ther.* 14, 5559–5574. doi:10.2147/DDDT.S240859
- Watson, D. J. G., Loiseau, F., Ingallinesi, M., Millan, M. J., Marsden, C. A., and Fone, K. C. F. (2012). Selective blockade of dopamine D3 receptors enhances while D2 receptor antagonism impairs social novelty discrimination and novel object recognition in rats: A key role for the prefrontal cortex. *Neuropsychopharmacology* 37 (3), 770–786. doi:10.1038/npp.2011.254
- Weinstein, J. J., Chohan, M. O., Slifstein, M., Kegeles, L. S., Moore, H., and Abi-Dargham, A. (2017). Pathway-specific dopamine abnormalities in schizophrenia. *Biol. Psychiatry* 81 (1), 31–42. doi:10.1016/j.biopsych.2016.03.2104
- Westbroek, I., van der Plas, A., de Rooij, K. E., Klein-Nulend, J., and Nijweide, P. J. (2001). Expression of serotonin receptors in bone. *J. Biol. Chem.* 276 (31), 28961–28968. doi:10.1074/jbc.M101824200
- Winship, I. R., Dursun, S. M., Baker, G. B., Balista, P. A., Kandratavicius, L., Maia-de-Oliveira, J. P., et al. (2019). An overview of animal models related to schizophrenia. *Can. J. Psychiatry* 64 (1), 5–17. doi:10.1177/0706743718773728
- Wysokiński, A., Kozłowska, E., Szczepocka, E., Łucka, A., Agier, J., Brzezińska-Błaszczak, E., et al. (2021). Expression of dopamine D1–4 and serotonin 5-HT_{1A}–3A receptors in blood mononuclear cells in schizophrenia. *Front. Psychiatry* 12, 645081. doi:10.3389/fpsy.2021.645081
- Yadav, V. K., Ryu, J. H., Suda, N., Tanaka, K. F., Gingrich, J. A., Schütz, G., et al. (2008). Lrp5 controls bone formation by inhibiting serotonin synthesis in the duodenum. *Cell* 135 (5), 825–837. doi:10.1016/j.cell.2008.09.059

- Yang, A. C., and Tsai, S.-J. (2017). New targets for schizophrenia treatment beyond the dopamine hypothesis. *Int. J. Mol. Sci.* 18 (8), 1689. doi:10.3390/ijms18081689
- Yang, H., Xu, Y., Zhu, M., Gu, Y., Zhang, W., Shao, H., et al. (2016). Inhibition of titanium-particle-induced inflammatory osteolysis after local administration of dopamine and suppression of osteoclastogenesis via D2-like receptor signaling pathway. *Biomaterials* 80, 1–10. doi:10.1016/j.biomaterials.2015.11.046
- Yun, H. M., Park, K. R., Hong, J. T., and Kim, E. C. (2016). Peripheral serotonin-mediated system suppresses bone development and regeneration via serotonin 6 G-protein-coupled receptor. *Sci. Rep.* 6, 30985. doi:10.1038/srep30985
- Zhang, L., and Shi, G. (2016). Gq-coupled receptors in autoimmunity. *J. Immunol. Res.* 2016, 3969023. doi:10.1155/2016/3969023
- Zhang, R., Edwards, J. R., Ko, S. Y., Dong, S., Liu, H., Oyajobi, B. O., et al. (2011). Transcriptional regulation of BMP2 expression by the PTH-CREB signaling pathway in osteoblasts. *PLoS One* 6 (6), e20780. doi:10.1371/journal.pone.0020780
- Zhao, J., Deng, Y., Jiang, Z., and Qing, H. G. (2016). G protein-coupled receptors (GPCRs) in alzheimer's disease: A focus on BACE1 related GPCRs. *Front. Aging Neurosci.* 8, 58. doi:10.3389/fnagi.2016.00058
- Zhong, X. P., and Xia, W. F. (2021). Regulation of bone metabolism mediated by β -adrenergic receptor and its clinical application. *World J. Clin. Cases* 9 (30), 8967–8973. doi:10.12998/wjcc.v9.i30.8967
- Zhu, J., Feng, C., Zhang, W., Wang, Z., Zhong, M., Tang, W., et al. (2022). Activation of dopamine receptor D1 promotes osteogenic differentiation and reduces glucocorticoid-induced bone loss by upregulating the ERK1/2 signaling pathway. *Mol. Med.* 28 (1), 23. doi:10.1186/s10020-022-00453-0
- Zhu, X., and Zheng, H. (2021). Factors influencing peak bone mass gain. *Front. Med.* 15 (1), 53–69. doi:10.1007/s11684-020-0748-y