Table 1. Summary of the FDA preclinical studies on the carcinogenic risk of marketed antidepressants.

Drug type[a]	Number of studies	Animals	Dose	Comments	(+)	MRHD	(−)
TCAs							
Imipramine	1	R	*Rats*: 90 mg/kg; 3 months	*Rats*: No evidence of carcinogenicity			X
SRIs							
Citalopram	2	M, R	*NMRI/BOM mice*: Up to 240 mg/kg/day; 18 months	*NMRI/BOM mice*: No evidence of carcinogenicity	X	1.3; 4×	X
			COBS WI rats: Up to 24 mg/kg/day; 24 months	*COBS WI rats*: Increased incidence of small intestine carcinoma (8 or 24 mg/kg/day)			
Escitalopram	2	M, R	*NMRI/BOM Mice*: Up to 240 mg/kg/die; 18 months	*NMRI/BOM Mice*: No evidence of carcinogenicity (up to 240 mg/kg/day)	X	NS	X
			COBS WI Rats: Up to 24 mg/kg/day; 24 months	*COBS WI Rats*: Increased incidence of small intestine carcinoma (8, 24 mg/kg/day)			
Fluoxetine	2	M, R	*Mice*: Up to 12 mg/kg/day; 2 years	*Mice*: No evidence of carcinogenicity			X
			Rats: Up to 10 mg/kg/day; 2 years	*Rats*: No evidence of carcinogenicity			X
Paroxetine	2	M, R	*Mice*: 1, 5, 25 mg/kg/day; 2 years	*Mice*: No drug-related increase in the number of mice with tumors	X	3.2×	X
			Rats: 1, 5, 20 mg/kg/day; 2 years	*Rats*: Increased incidence of reticulum cell sarcomas, lymphoreticular tumors (♂)			
Sertraline	2	M, R	*CD-1 mice*: Up to 40 mg/kg/day; lifetime	*CD-1 mice*: Dose-related increased incidence of liver adenomas (♂)	X	0.25–1.0×	
			Long-Evans rats: Up to 40 mg/kg/day; lifetime	*Long-Evans rats*: Increased incidence of follicular adenomas of the thyroid (♀); increased incidence of uterine adenocarcinomas	X	2×	
						0.5–2.0×	
SNRIs							

Drug type[a]	Number of studies	Animals	Dose	Comments	(+)	MRHD	(−)
Duloxetine	2	M, R	*Mice*: Up to 140 mg/kg/day (♀); 2 years; up to 100 mg/kg/day (♂); 2 years	*Mice*: Increased incidence of hepatocellular adenomas and carcinomas (♀)	X	11×	X
			Rats: Up to 27 mg/kg/day (♀); 2 years; up to 36 mg/kg/day (♂); 2 years	*Rats*: No evidence of carcinogenicity			
Venlafaxine	2	M, R	*Mice*: Up to 120 mg/kg/day; 18 months	*Mice*: No evidence of carcinogenicity			X
			Rats: Up to 120 mg/kg/day; 24 months	*Rats*: No evidence of carcinogenicity			X
NaSSAs							
Mirtazapine	2	M, R	*Mice*: 2, 20, 200 mg/kg/day; 2 years	*Mice*: Increased incidence of hepatocellular adenoma and carcinoma in (♂) at the high dose	X	12×	
			Rats: 2, 20, 60 mg/kg/day; 2 years	*Rats*: Increased incidence of hepatocellular adenoma at the mid/high doses (♀), hepatocellular tumors, thyroid follicular adenoma/cystadenoma and carcinoma at the high dose (♂)	X	45×	
SARIs							
Trazodone	1	R	*Rats*: 300 mg/kg/day; 18 months	*Rats*: No evidence of carcinogenicity			X
Atypical antidepressants							
Bupropion	2	M, R	*Mice*: Up to 150 mg/kg/day; lifetime	*Mice*: No evidence of carcinogenicity	X	2–7×	X
			Rats: Up to 300 mg/kg/day; lifetime	*Rats*: Increased incidence of nodular proliferative liver lesions			
Total number of positive and negative studies					9		11

FDA: US Food and Drug Administration; R: rats; M: mice; NS: not specified; ♂: male; ♀: female; MRHD: maximum recommended human dose on a mg/m^2 basis; (+): total number of positive studies; (−): total number of negative studies; TCAs: tricyclic antidepressants; SRIs: serotonin

reuptake inhibitors; SNRIs: serotonin-norepinephrine reuptake inhibitors; NaSSAs: noradrenergic and specific serotonergic antidepressants; SARIs: serotonin antagonist and reuptake inhibitors.

No data were available for amitriptyline, desipramine, nortriptyline (TCAs), phenelzine and tranylcypromine (monoamine oxidase inhibitors—MAOIs).

a
Center for Drug Evaluation and Research (n.d.).

Table 2. Summary of the FDA preclinical studies on the carcinogenic risk of marketed antipsychotics.

Drug type[a]	Number of studies	Animals	Dose	Comments	(+)	MRHD	(−)
Typical antipsychotics							
Haloperidol	2	M, R	*Albino Swiss mice*: Up to 5 mg/kg/day; 18 months	*Mice*: Increased incidence in mammary gland neoplasia and total tumor incidence at 5 and 20 times the highest initial daily dose (♀); increased incidence in pituitary gland neoplasia at 20 times the same daily dose (♀)	X	NS	X
			Wistar rats: Up to 5 mg/kg/day; 24 months	*Rats*: No evidence of carcinogenicity			
Atypical antipsychotics							
Aripiprazole	3	M, R	*ICR mice*: 1, 3, 10, 30 mg/kg/day lifetime	*ICR mice*: Increased incidence of pituitary gland adenomas, mammary gland adenocarcinomas and adenoacanthomas (♀; prolactin-mediated)	X	0.1–0.9×	
			SD rats: 1, 3, 10 mg/kg/day lifetime	*SD and F344 rats*: Increased incidence of mammary gland fibroadenomas (♀) (10 mg/kg/day), adrenocortical carcinomas and combined adrenocortical adenomas/carcinomas (♀) (60 mg/kg/day)	X	0.1×	
			F344 rats: 10, 20, 40, 60 mg/kg/day; 2 years		X	14×	
Asenapine	2	M, R	*Mice*: 10 mg twice daily, lifetime	*Mice*: Increased incidence of malignant lymphomas (♀)	X	1.5× (PL)	X
			SD rats: lifetime	*SD rats*: No evidence of carcinogenicity			

Drug type[a]	Number of studies	Animals	Dose	Comments	(+)	MRHD	(−)
Clozapine	2	M, R	*Mice*: Up to 900 mg/day	*Mice*: No evidence of carcinogenicity			X
			Rats: Up to 900 mg/day	*Rats*: No evidence of carcinogenicity			X
Iloperidone	3	M, R	*CD-1 mice*: 2.5, 5, 10 mg/kg/day	*CD-1 mice*: Increased incidence of malignant mammary gland tumors in ♀ (prolactin-mediated) (2.5 mg/kg/day)	X	0.5×	X
			SD rats: 4, 8, 16 mg/kg/day	*SD rats*: No evidence of carcinogenicity	X	0.4; 3; 23× (PL)	
			Wistar rats: 25, 75, 200 mg/kg/day in ♂ and 50, 150, 250 mg/kg/day in ♀ (metabolite P95)	*Wistar rats*: Drug-related neoplastic changes occurred in ♂, in the pituitary gland at all doses and in the pancreas at the high dose (prolactin-mediated)			
Lurasidone	2	M, R	*Mice*: 30, 100, 300, 650 mg/kg/day	*Mice*: Increased incidence of malignant mammary gland tumors and pituitary gland adenomas (F; prolactin-mediated)	X	14×	
			Rats: 12, 36 mg/kg/day lifetime	*Rats*: Increased incidence of mammary gland carcinomas (♀; prolactin-mediated)	X	6×	
Olanzapine	3	M, R	*Mice*: 3, 10, 30/20 mg/kg/day (♂); 0.25, 2, 8 mg/kg/day (♀); 78 weeks	*Mice*: Increased incidence of liver hemangiomas and hemangiosarcomas (♀)	X	2×	X
			Rats: 0.25, 1, 2.5, 4 mg/kg/day (♂); 0.25, 1, 4, 8 (♀); 2 years	*Mice*: No evidence of carcinogenicity	X	0.5–2×	
				Rats: Increased incidence of mammary gland adenomas, adenocarcinomas (♀; prolactin-mediated)			
Quetiapine	2	M, R	*C57BL mice*: 20, 75, 250, 750 mg/kg/day; 2 years	*C57BL mice*: Increased incidence of thyroid gland follicular adenomas (♂)	X	1.5, 4.5×	

Drug type[a]	Number of studies	Animals	Dose	Comments	(+)	MRHD	(−)
			Wistar rats: 25, 75, 250 mg/kg/day; 2 years	*Wistar rats*: Increased incidence of mammary gland adenocarcinomas (♀; prolactin-mediated)	X	0.3; 1; 3×	
Risperidone	2	M, R	*Albino Swiss mice*: 0.63, 2.5, 10 mg/kg/day; 18 months	*Albino Swiss mice*: Increased incidence in pituitary gland adenomas, mammary gland adenocarcinomas (♀; prolactin-mediated)	X	0.2; 0.75; 3×	
			Wistar rats: 0.63, 2.5, 10 mg/kg/day; 25 months	*Wistar rats*: Increased incidence in endocrine pancreas adenomas (♂), mammary gland adenocarcinomas (♂, ♀; prolactin-mediated)	X	0.4; 1.5; 6×	
Ziprasidone	2	M, R	*CD-1 mice*: 2, 6, 12 mg/kg/day; 24 months	*CD-1 mice*: Dose-related increased incidence of pituitary gland adenoma and carcinoma and mammary gland adenocarcinoma at all doses tested	X	1–5×	X
			Long-Evans rats: 2, 6, 12 mg/kg/day; 24 months	*Long-Evans rats*: No evidence of carcinogenicity			
Total number of positive and negative studies					16		7

FDA: US Food and Drug Administration; R: rats; M: mice; NS: not specified; ♂: male; ♀: female; PL: plasma levels; SD: Sprague-Dawley; MRHD: maximum recommended human dose on a mg/m^2 basis; (+): total number of positive studies; (−): total number of negative studies.

No data were available for chlorpromazine (typical antipsychotic) and paliperidone (atypical antipsychotic).

a
Center for Drug Evaluation and Research (n.d.).

Table 3. Summary of the FDA preclinical studies on the carcinogenic risk of marketed benzodiazepines and sedative-hypnotics.

Drug type[a]	Number of studies	Animals	Dose	Comments	(+)	MRHD	(−)
Benzodiazepines							
Alprazolam	2	M, R	*Mice*: 10 mg/kg/day; 2 years	*Mice*: No evidence of carcinogenicity			X
			Rats: 50 mg/kg/day; 2 years	*Rats*: No evidence of carcinogenicity			X

Drug type[a]	Number of studies	Animals	Dose	Comments	(+)	MRHD	(−)
Clobazam	1	R	*Rats*: 4, 20, 100 mg/kg/day; 2 years	*Rats*: Increased incidence of thyroid follicular cell adenomas (♂, high dose)	X	NS	
Diazepam	2	M, R	*Mice*: 75 mg/kg/day; 80 weeks	*Mice*: Increased incidence of liver tumors in ♂	X	6×	
			Rats: 75 mg/kg/day; 2 years	*Rats*: Increased incidence of liver tumors in ♂	X	12×	
Lorazepam	1	R	*Rats*: 18 months	*Rats*: No evidence of carcinogenicity			X
Midazolam	2	M, R	*Mice*: 1, 9, 80 mg/kg/day; 2 years	*Mice*: Increased incidence of hepatic tumors in ♀	X	NS	
			Rats: 1, 9, 80 mg/kg/day; 2 years	*Rats*: Increased incidence in benign thyroid follicular cell tumors (♂) at the highest dose tested	X	NS	
Oxazepam	2	R	*Mice*: 9 months	*Mice*: Increased incidence of liver adenomas and carcinomas	X	35–100×	
			Rats: 2 years	*Rats*: Increased incidence in benign thyroid follicular cell tumors, testicular interstitial cell adenomas, prostatic adenomas	X	30×	
Triazolam	1	M	*Mice*: 24 months	*Mice*: No evidence of carcinogenicity			X
Sedative-hypnotics							
Eszopiclone	5	M, R	*Mice*: Racemic zopiclone; 1, 10, 100 mg/kg/day; 2 years	*Mice*: Increases in pulmonary carcinomas and carcinomas plus adenomas (♀) and skin fibromas and sarcomas (♂) at the highest dose tested	X	90× (PL)	X
			Mice: 100 mg/kg/day p53 ± transgenic mice: 300 mg/kg/day	*Mice*: No increased incidence in either pulmonary or skin tumors *p53 ± transgenic mice*: No evidence of carcinogenicity	X	150× (PL)	X
			Rats: 16 mg/kg/day; 104 weeks in ♀; 97 weeks in ♂	*Rats*: No evidence of carcinogenicity		70× (PL)	X
			Rats: 1, 10, 100 mg/kg/day; 2 years	*Rats*: Increased incidence in mammary gland adenocarcinomas (♀) and			

Drug type[a]	Number of studies	Animals	Dose	Comments	(+)	MRHD	(−)
				thyroid gland follicular cell adenomas and carcinomas (♂) at the highest dose tested			
Zaleplon	2	M, R	*Mice*: 25, 50, 100, 200 mg/kg/day; 2 years	*Mice*: Increased incidence of hepatocellular adenomas in ♀ in the high-dose group	X	49×	X
			Rats: 1, 10, 20 mg/kg/day; 2 years	*Rats*: No evidence of carcinogenicity			
Zolpidem	2	M, R	*Mice*: 4, 18, 80 mg/kg/day; 2 years	*Mice*: No evidence of carcinogenicity	X	115×	X
			Rats: 4, 18, 80 mg/kg/day; 2 years	*Rats*: Renal liposarcomas in 4/100 rats (3♂, 1 ♀) receiving 80 mg/kg/day and 1 renal lipoma (♂) at the 18 mg/kg/day dose		6×	
Total number of positive and negative studies					11		9

FDA: US Food and Drug Administration; R: rats; M: mice; NS: not specified; ♂: male; ♀: female; PL: plasma levels; MRHD: maximum recommended human dose on a mg/m^2 basis; (+): total number of positive studies; (−): total number of negative studies.

No data were available for bromazepam, clonazepam (benzodiazepine) and chlordiazepoxide (sedative-hypnotic).

a
Center for Drug Evaluation and Research (n.d.).

Table 4. Summary of the FDA preclinical studies on the carcinogenic risk of marketed amphetamines and stimulants.

Drug type[a]	Number of studies	Animals	Dose	Comments	(+)	MRHD	(−)
Amphetamines							
Amphetamine[b]	2	M, R	*Mice*: Up to 30 mg/kg/day in ♂, up to 19 mg/kg/day in ♀; 2 years	*Mice*: No evidence of carcinogenicity			X
			Rats: Up to 5 mg/kg/day; 2 years	*Rats*: No evidence of carcinogenicity			X
Methylphenidate	3	M, R	*B6C3F1 mice*: 60 mg/kg/day lifetime	*B6C3F1 mice*: Increased incidence of hepatocellular adenomas and hepatoblastomas (♂)	X	30–4×	X
			F344 rats: 45	*F344 rats*: No			X

Drug type[a]	Number of studies	Animals	Dose	Comments	(+)	MRHD	(−)
			mg/kg/day lifetime	evidence of carcinogenicity			
			p53 ± *transgenic mice*: 60–74 mg/kg/day; 24 weeks	*p53* ± *transgenic mice*: No evidence of carcinogenicity			
Stimulants							
Modafinil	3	M, R	*Mice*: 6, 30, 60 mg/kg/day; 78 weeks	*Mice*: No evidence of carcinogenicity			X
			Tg.AC transgenic mice: 125, 250, 500 mg/kg/day administered dermally	*Tg.AC transgenic mice*: No evidence of carcinogenicity			X
			Rats: 6, 30, 60 mg/kg/day; 104 weeks	*Rats*: No evidence of carcinogenicity			X
NRI							
Atomoxetine	2	M, R	*Mice*: Up to 458 mg/kg/day; 2 years	*Mice*: No evidence of carcinogenicity			X
			Rats: Up to 47 mg/kg/day (8–5× MRHD); 2 years	*Rats*: No evidence of carcinogenicity			X
Total number of positive and negative studies					1		9

FDA: US Food and Drug Administration; NT: not tested; R: rats; M: mice; ♂: male; ♀: female; MRHD: maximum recommended human dose on a mg/m^2 basis; (+): total number of positive studies; (−): total number of negative studies; NRI: norepinephrine reuptake inhibitor.

No data were available for dextroamphetamine, hydroxyamphetamine and methamphetamine (amphetamines).

a
Center for Drug Evaluation and Research (n.d.).
b
Combination of the neutral sulfate salts of dextroamphetamine and amphetamine, with the dextro isomer of amphetamine saccarate and d, l-amphetamine aspartate monohydrate.

Table 5. Summary of the FDA preclinical studies on the carcinogenic risk of marketed anticonvulsants.

Drug type[a]	Number of studies	Animals	Dose	Comments	(+)	MRHD	(−)
Anticonvulsants							
Carbamazepine	1	R	*Mice*: 25, 75,	*Mice*: Dose-related	X	NS	

Drug type[a]	Number of studies	Animals	Dose	Comments	(+)	MRHD	(−)
			250 mg/kg/day; 2 years	increased incidence of hepatocellular tumors in ♀ and benign interstitial cell adenomas in the testes of ♂			
Gabapentin	2	M, R	*Mice*: 200, 600, 2000 mg/kg/day; 2 years	*Mice*: No evidence of carcinogenicity	X	NS	X
			Rats: 250, 1000, 2000 mg/kg/day; 2 years	*Rats*: Increased incidence of pancreatic acinar cell adenomas and carcinomas in ♂ receiving the high dose			
Lamotrigine	3	M, R	*Mice*: 30 mg/kg/day; 2 years	*Mice and rats*: No evidence of carcinogenicity			X X X
			Rats: 10–15 mg/kg/day (equivalent to 90 mg/m^2 and 60 to 90 mg/m^2); 2 years				
Oxcarbazepine	3	M, R	*Mice*: Up to 100 mg/kg/day; 2 years	*Mice*: Dose-related increased incidence of hepatocellular adenomas (⩾70 mg/kg/day)	X	0.1×	
			Rats: Up to 250 mg/kg/day; 10-MHD up to 600 mg/kg/day; 2 years	*Rats*: Increased incidence of hepatocellular carcinomas in ♀ (⩾25 mg/kg/day)	X	0.1×	
				Increased incidence of hepatocellular adenomas and/or carcinomas in ♂ and ♀ treated with MHD (600 mg/kg/day)	X	2.4×	
				Increased incidence of benign testicular interstitial cell tumors in ♂ at 250 mg oxcarbamazepine/kg/day and at ⩾250 mg MHD/kg/day; tncreased incidence of granular cervix and vagina in ♀ at 600 mg			

Drug type[a]	Number of studies	Animals	Dose	Comments	(+)	MRHD	(−)
				MHD/kg/day			
Pregabalin	2	M, R	*Mice*: Up to 5000 mg/kg; 2 years	*Mice*: Dose-dependent increased incidence of hemangiosarcomas in mice (200, 1000 or 5000 mg/kg)	X	=MRHD	X
			Rats: Up to 450 mg/kg in ♂, up to 900 mg/kg in ♀; 2 years	*Rats*: No evidence of carcinogenicity			
Topiramate	2	M, R	*Mice*: 20, 75 and 300 mg/kg; 21 months	*Mice*: Increased incidence in urinary bladder tumors (20, 75 and 300 mg/kg), statistically significant in ♂ and ♀ receiving 300 mg/kg	X	0.5–1×	X
			Rats: Up to 120 mg/kg; 2 years	*Rats*: No evidence of carcinogenicity			
Valproate	2	M, R	*Mice and Rats*: 80, 170 mg/kg/day; 2 years	*Mice*: Dose-related trend for benign pulmonary adenomas in ♂	X	<MRHD	
				Rats: Increased incidence of subcutaneous fibrosarcomas in high-dose ♂	X	<MRHD	