

**Table S1. Cell-Based and In Vivo Pharmacology Studies Supporting Serotonergic Activity of Fenfluramine or Major Metabolite Norfenfluramine**

Receptor (Reference)	FFA or NFA activity	Model(s)	G-protein coupling	Second messenger response to FFA or NFA	Predicted cellular response to FFA or NFA
5-HT1D (1)	Confirmed agonist	Cell-based pharmacology; DS mouse; MES mouse; DS zebrafish	Coupled to Gi/Go	Decreased cellular levels of cAMP	Inhibitory
5-HT2A (1-3)	Confirmed agonist	Cell-based pharmacology; MES mouse; DS zebrafish; SUDEP mouse <sup>a</sup>	Coupled to Gq/G11	Increased cellular levels of IP <sub>3</sub> and DAG	Excitatory
5-HT2B (4,7)	Confirmed agonist	Cell-based pharmacology <sup>b</sup>	Coupled to Gq/G11	Increased cellular levels of IP <sub>3</sub> and DAG	Excitatory
5-HT2C (1,4-6)	Confirmed agonist	Cell-based pharmacology; DS zebrafish	Coupled to Gq/G11	Increased cellular levels of IP <sub>3</sub> and DAG	Excitatory
5-HT4 (5,6)	Potential agonist	SUDEP mouse	Coupled to Gs	Increased cellular levels of cAMP	Excitatory
5-HT1A (2,3,5,6)	Potential antagonist	Cell-based pharmacology; SUDEP mouse	Coupled to Gi/Go	Increased cellular levels of cAMP	Excitatory
Additional Serotonergic Mechanisms					
Target	Activity	Model(s)	Mechanism		Predicted cellular response
5-HT releaser (8)	Increased 5-HT release into synaptic cleft	Cell-based assays; Xenopus oocytes In vivo rat	SERT substrate, reverse transporter		Excitatory

Cell-based pharmacology agonist assays found no activity at 5-HT1B, 5-HT1E, 5-HT1F, 5-HT3, 5-HT5A, 5-HT6, and 5-HT7.

<sup>a</sup>5-HT2 antagonist (ritanserin) enhanced FFA-mediated reduction in seizures and SUDEP; these data contradict cell-based pharmacology, MES mouse, and DS zebrafish in vivo data.

<sup>b</sup>5-HT2B was not active in DS zebrafish model.

DAG, diacylglycerol; DS, Dravet syndrome; FFA, fenfluramine; IP<sub>3</sub>, inositol triphosphate; MES, maximal electroshock seizure model; NFA, norfenfluramine; SUDEP, sudden unexpected death in epilepsy.

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