

Authors	Year	Sample	Resistance criteria	Modality	Medication at time of scan	Diagnostic Criteria
Ahmed et al. ¹	2015	33 TR, 31 HC	Failed ≥ 2 Aps (≥ 1 atypical). Prolonged positive or negative symptoms of \geq moderate severity	MRI – Structural	Pre and post clozapine	DSM-IV-TR
Alonso-Solis et al. ²	2015	19 TR-AVH, 14 R, 20 HC	Daily AVH AND failed ≥ 2 Aps (at dose equiv ≥ 600 mg clozapine/day)	fMRI – resting state	Typical/Atypical Aps	DSM-IV-TR
Anderson et al. ³	2015	15 CNR, 19 TR, 18 R, 20 HC	Lack of significant response despite trials (adequate dose and ≥ 6 wk duration) of ≥ 2 Aps	MRI- structural	Atypical Aps (including clozapine)	DSM-IV-TR
Arango et al. ⁴	2003	45 TR	Residual positive (≥ 8 BPRS psychotic) or negative symptoms (≥ 20 SANS) despite ≥ 2 6wk AP trials. Prospective trial fluphenazine 20mg/day – subjects with $>30\%$ improvement excluded.	MRI – Structural	Clozapine or Haloperidol	DSM-III-R
Bartlett et al. ⁵	1998	7 TR, 7 R	Unmedicated BPRS ≥ 50 or medicated BPRS ≥ 42 AND no worsening when unmedicated. Prospective 4-wk AP trial for patients with no records	FDG-PET (haloperidol challenge)	Not specified	DSM-III-R
Buchsbaum et al. ⁶	1992	12 Scz	Not specified	FDG-PET	Pre/post clozapine/thioxene	Not specified
Cachia et al. ⁷	2008	30 TR-AVH, 28 HC	Kane et al (1988)	MRI-Structural	Typical /atypical Aps	DSM-IV
Chakos et al. ⁸	1995	8 clozapine, 7 typical Aps	Not specified	MRI- Structural	Clozapine and typical Aps	Not specified
Demjaha et al. ⁹	2012	12 TR, 12 R, 12 HC	Conley et al (2001)	FDOPA-PET	Non clozapine Aps	DSM-IV
Demjaha et al. ¹⁰	2014	6 TR, 8 R, 10 HC	Conley et al (2001)	1H-MRS	Typical and atypical Aps	DSM-IV
Ergun et al. ¹¹	2010	20 TR	Treatment refractory or AP intolerant	^{99m} Tc-HMPAO SPECT	Pre and post clozapine	DSM-IV
Ertugrul et al. ¹²	2009	22 TR	On clozapine due to treatment resistance or intolerance to previous Aps	^{99m} Tc-HMPAO SPECT/ 1H-MRS	Typical and atypical Aps	DSM-IV
Fitzgerald et al. ¹³	2007	3 TR, 4HC	Persistent severe refractory hallucinations that had not responded to ≥ 2 adequate courses of Aps	fMRI (word generation task)	Clozapine, amisulpride, sertraline, valproate, diazepam	Not specified
Friedman et al. ¹⁴	1991	34 TR	Failure to respond to ≥ 2 different class Aps (each for ≥ 6 weeks, ≥ 800 mg CPZ equiv). ≥ 4 on BPRS positive items	CT Scan	Clozapine	RDC
Galletly et al. ¹⁵	2005	15 TR, 14 HC	Not specified	EEG	Pre and post clozapine	DSM-IV
Goldstein et al. ¹⁶	2015	11 CNR, 16 TR, 15 R, 11 HC	NICE (2002), RANZCP (2005)	1H-MRS	Atypical Aps including clozapine	DSM-IV
Gross et al. ¹⁷	2004	16 TR	Kane et al (1988)	EEG	Risperidone or olanzapine	SCID + chart review
Holleran et al. ¹⁸	2014	19 TR, 19 HC	Failure to respond to ≥ 2 Aps (≥ 1 atypical), prolonged moderate/severe positive or negative symptoms.	MRI- DTI	Atypical Aps, antidepressants	DSM-IV
Honer et al. ¹⁹	1995	42 TR (inc 3 Schizoaffective)	Poor response to adequate AP dose for ≥ 6 months. May et al. (1988) scale.	CT scan	Antipsychotic class not specified	DSM-III-R
Hoptman et al. ²⁰	2005	49 TR	Kane et al (1988)	MRI-Structural	Typical and atypical Aps (including clozapine)	SCID + chart review
Horton et al. ²¹	2011	21 TR, 19 HC	Not specified	EEG	Clozapine	DSM-IV and SCID
Kikuchi et al. ²²	2014	26 TR	Poor tolerance or poor response despite ≥ 2 Aps (≥ 1 atypical), ≥ 4 weeks and ≥ 600 mg CPZ equiv.	EEG	Pre and post clozapine treatment	Not specified
Klirova et al. ²³	2013	15 TR-AVH, 19HC	Non response to both typical and atypical Aps + ≥ 5 episodes AVH per day in the last month	FDG PET	Aps, Antidepressants, anticonvulsants	DSM-IV
Knott et al. ²⁴	2001	17 TR, 17 HC	Kane et al (1988)	EEG	Not specified	DSM-III-R
Knott et al. ²⁵	2002	17 TR	Kane et al (1988)	EEG	Pre/post clozapine	DSM-III-R
Konicki et al. ²⁶	2001	TR 26	Kane et al (1988)	CT scan	clozapine	DSM-III-R
Kubera et al. ²⁷	2014	10 TR-AVH, 10 nAVH, 14 HC	Persistent AVH despite ≥ 2 AP trials (adequate dose, ≥ 6 wks)	MRI Structural	Clozapine and other Aps	DSM-IV
Lacroix et al. ²⁸	1995	10 TR, 10 NR	35% or more and a 30% or less reduction, respectively, on the Brief Psychiatric Rating Scale (BPRS)	EEG	Not specified	DSM-IV

Lahti et al. ^{29,30}	2003, 2004	6 partially responsive, 10 HV	Not specified	¹⁵ O-PET	Pre/post clozapine	DSM-III-R
Lauriello et al. ³¹	1998	21 TR	Treatment intolerant or inadequate response.	MRI-Structural	Typical Aps	DSM-III-R
Lawrie et al. ³²	1995	20 TR, 20 R	May et al (1988)	MRI-Structural/ SPECT	Not specified	DSM-IV
Lee et al. ^{33,34}	2006, 2008	25 TR-AVH, 23 nAVH	Persistent AVH for ≥2yrs	EEG	Conventional neuroleptics	DSM-IV
Maller et al. ³⁵	2012	52 TR, 182 MDD, 76 HC	Not specified	MRI-Structural	Not specified	DSM-IV
MacCrimmon et al. ³⁶	2012	64 TR	Kane et al (1988)	EEG	Pre/post clozapine, (+ other psychotropics)	DSM-IV
Milovan et al. ³⁷	2004	13TR, 13 HC	Kane et al (1988)	EEG	Not specified	DSM-IV
Mitelman et al. ³⁸	2005	13 TR, 24 R, 27 HC	Keefe et al (1987)	MRI-Structural	Not specified	DSM-IV
Molina et al. ³⁹	1996	24 TR	Lack of adequate response to ≥2 chemically different Aps, ≥800mg CPZ equiv	^{99m} Tc-HMPAO SPECT	Pre/post clozapine	DSM-IV
Molina et al. ⁴⁰	1997a	36 TR, 28 HC	Kane et al (1988)	^{99m} Tc-HMPAO SPECT	Not specified	DSM-IV-R
Molina et al. ⁴¹	1997 b	39 TR (includes Molina et al. 1996 sample), 28 HC	Lack of response to ≥2 dissimilar Aps (≥800mg CPZ equiv), each one for ≥2 months over last year.	^{99m} Tc-HMPAO SPECT	Pre/post clozapine	DSM-IV
Molina et al. ⁴²	2003	25 TR	Lack of response to ≥2 different Aps for ≥6 weeks in past 12 mths, dose ≥800mg CPZ equiv. Significant positive or disorganisation residual symptoms	MRI-structural FDG PET	Pre/post clozapine	DSM-III-R
Molina et al. ^{43,44}	2005, 2007	23 TR, 17NN, 18HC	Lack of adequate response to ≥2 Aps for ≥4 weeks in preceding 12 months, dose ≥800mg CPZ equiv. All had haloperidol for ≥4wks before scan	FDG PET	Pre/post clozapine	DSM-IV
Molina et al. ⁴⁵	2008a	30 TR, 19 R and 44 HC	Kane et al (1988)	MRI-structural, EEG	Haloperidol prior to first MRI, then olanzapine or clozapine	DSM-IV
Molina et al. ⁴⁶	2008b	10 TR, 10 HC	A poor response during the previous year to haloperidol or risperidone followed by lack of response to 4 week trial of risperidone	^{99m} Tc-HMPAO SPECT	Pre/post clozapine	DSM-IV
Potkin et al. ⁴⁷	1994	18 Scz	Not specified	FDG PET	Pre/post clozapine	Not specified
Potkin et al. ⁴⁸	2003	15 TR	Not specified	FDG PET	Not specified	DSM-IV
Quarantelli et al. ⁴⁹	2014	20 (TR + CNR), 15 R, 16 HC	<20 % improvement AND total > 45 on BPRS AND ≥4 in ≥2 BPRS psychotic items AND ≥2 yrs poor functioning despite 6-8 weeks with ≥2 Aps and good adherence.	MRI –structural	Typical and atypical Aps (including clozapine)	DSM-IV-TR
Ramos et al. ⁵⁰	2001	10 TR, 10 R	Keefe et al (1990) and Brenner & Merlo (1995) criteria	EEG	Not specified	DSM-IV
Ravan et al. ⁵¹	2015	47 TR, 66 HC	Kane et al (1988) criteria	EEG (auditory evoked)	Pre/Post clozapine	DSM-IV
Scheepers et al. ⁵²	2001a	26 TR	No response (CGI≥4) to ≥1 typical AP for ≥ 4 weeks OR severe EPSEs or TD	MRI-Structural	Pre/post clozapine	DSM-IV
Scheepers et al. ⁵³	2001 b	28 TR	No response (CGI≥4) to ≥1 typical AP for ≥ 4 weeks OR severe EPSEs or TD	MRI-Structural	Pre/post clozapine	DSM-IV
Sun et al. ⁵⁴	2009	42 TR, 42 MDD, 30 HC	Kane et al (1988) criteria	MRI-Structural	Clozapine	DSM-III-R
Tsekou et al. ⁵⁵	2015	7 TR	Bremner et al (1990) criteria AND ≥70 on PANSS, and schizophrenia diagnosis for ≥2 years	Sleep EEG	Pre/post clozapine	DSM-III-R
Umbricht et al. ⁵⁶	1998	11 TR, 6 R, 13 HC	Partially refractory –≥4 on any of the 4 BPRS positive symptom items	EEG	Clozapine and haloperidol	DSM-III-R
Vercammen et al. ⁵⁷	2010	27 TR-AVH, 27 HC	Daily AVH, ≥2 adequate AP trials	MRI-Resting state	Aps and benzodiazepines	DSM-IV
Wolf et al. ^{58,59}	2011, 2012	10 TR-AVH, 10 R, 14 HC	Kane et al (1988)	MRI-Resting state	Clozapine	DSM-IV
Zhao et al. ⁶⁰	2006	21 TR, 40 HC	Andreason's negative symptom profile	SPECT	Medication free, follow up on clozapine	DSM-IV
Zugman et al. ⁶¹	2013	61 TR, 67 R, 80 HC	Kane et al (1988)	MRI-Structural	Typical and atypical Aps (including clozapine)	DSM-IV

Table 1: Study characteristics

1H-MRS – proton magnetic resonance spectroscopy; AP –antipsychotic; AVH – Auditory verbal hallucinations; BPRS – Brief Psychiatric Rating Scale; CNR – clozapine non responder; CPZ equiv – Chlorpromazine equivalents; DSM – Diagnostic and Statistical Manual of Mental Disorders; EEG – electroencephalogram; HC- healthy controls; MDD – major depressive disorder; MRI – Magnetic Resonance Imaging; PET – Positron Emission Tomography; Individuals with schizophrenia without auditory hallucinations; R – antipsychotic responders; Scz- unspecified whether responder/resistant; SPECT- Single-photon emission computed tomography

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