Appendix 2: Levels of evidence and grades of recommendation used to describe the strength of recommendations in clinical practice guidelines (CPG) addressing the pharmacological treatment of first episode schizophrenia.

PORT 2009	Spain 2009	Malaysia, 2009	Singapore 2011	BAP 2011	WFSBP, 2012	SIGN, 2013	Harvard 2013	NICE 2014	RANZCP, 2016
Must have at least 2	Ia Meta-analysis of	Level 1, good	1++ High quality	Causal	Category of	1++ High quality	None described	Strength of	Recommendations
RCTs to make a	RCTs	strength, Meta-	meta- analysis,	relationships and	Evidence:	meta- analysis,		recommendation	are either Evidence
recommendation		analysis of RCT,	systematic reviews	treatment	A: Full evidence	systematic reviews		described in the	based (EBR) or
	Ib At least one RCT	systematic review.	of RCTs or RCT with	Category I; Meta-	from controlled	of RCTs or RCT with		language of the	consensus based
			very low risk of bias.	analysis of RCTs, at	studies:	very low risk of bias.		recommendation.	(CBR).
	IIa At least one well	Level 2, good		least one large good	Two or more double				
	designed non-	strength. Large	1+ Well-conducted	quality RCT or	blind RCT vs placebo	1+ Well-conducted		Must or must not:	The level of
	randomised	sample RCT	meta-analysis,	replicated, smaller	and one or more	meta-analysis,		Legal duty to apply	evidence on which
	controlled		systematic reviews	RCTs.	RCT vs active	systematic reviews		recommendation of	EBR is according to
	prospective study	Level 3, Good to fair	of RCTs or RCTS		comparator with	of RCTs or RCTS		if consequences of	the National Health
		strength. Small	with a low risk of	Category II: Small	placebo arm or well	with a low risk of		not following	and Medical
	IIb At least one well	sample RCT.	bias	non-replicated RCT;	conducted non-	bias		recommendation	Research Council's
	designed quasi-			at least one	inferiority trial. If			are serious or life	levels of evidence
	experimental study	Level 4, Good to fair	 Meta-analysis, 	controlled study or	there is an existing	1- Meta-analysis,		threatening.	for healthcare
		strength. Non-	systematic reviews	at least one other	negative study it	systematic reviews			interventions.
	III Well designed	randomised	of RCTs or RCTs with	quasi experimental	must be outweighed	of RCTs or RCTs with		Should or should	
	observational	controlled	a high risk of bias	study. RCT must	by at least 2 positive	a high risk of bias		not:	Level I: A systematic
	studies eg	prospective trial.		have a control	studies or a meta-			Indicates a strong	review of level II
	comparative study,		2++ High quality	treatment arm.	analysis.	2++ High quality		recommendation.	studies.
	correlation study or	Level 5, fair	systematic reviews			systematic reviews		'Offer', 'refer',	
	case-control studies	strength. Non-	of case control or	Category III: non-	B: Limited positive	of case control or		'advise' when	Level II: A
		randomised	cohort studies, High	experimental	evidence from	cohort studies, High		confident that for	randomised
	IV Expert opinion	controlled	quality case control	descriptive studies	controlled studies.	quality case control		the vast majority of	controlled trial.
	and clinical	prospective trial	or cohort studies	eg comparative,	One or more RCT	or cohort studies		patients an	
	experience	with historical	with a very low risk	correlation or case	showing superiority	with a very low risk		intervention will do	Level III-1: A
		control.	of bias or	control.	to placebo or RCT vs	of bias or		more good than	pseudo-randomised
	Grade A: Evidence		confounding and a		comparator without	confounding and a		harm and be cost	controlled trial.
	level 1a or 1b. At	Level 6. Fair	high probability that	Category (IV) Expert	placebo control and	high probability that		effective.	
	least one good	strength. Cohort	the relationship is	committee report/	no negative studies	the relationship is		Conversely 'do not	Level III-2: A
	quality RCT.	study.	causal	opinion/ clinical	exist.	causal		offer' when	comparative study
				experience				confident that	with concurrent
	Grade B: Evidence	Level 7, Poor	2+ Well conducted		C Evidence from	2+ Well conducted		intervention will not	controls: non-
	level IIa, IIb, or III.	strength, case-	case control or	Non-causal	Uncontrolled	case control or		be of benefit for	randomised,
	Methodologically	controlled study.	cohort studies with	relationships	studies/ case	cohort studies with		most patients.	experimental trial.
	correct clinical trials		a low risk of bias or	Category I: Evidence	reports/ expert	a low risk of bias or			Cohort studies.
	that are not RCTs	Level 8, Poor	confounding and a	from large	opinion.	confounding and a		Could be used.	Case-control study.
		strength, Non-	moderate	representative	C1: Uncontrolled	moderate		'Consider' if	Interrupted time-
	Grade C: Evidence	controlled clinical	probability that the	population samples.	studies: 1 or more	probability that the		confident that an	series with a control
	level IV. Expert	series, descriptive	relationship is		positive naturalistic	relationship is		intervention will do	group.
	opinion in the	studies multi-centre	causal.	Category II:	study, comparison	causal.		more good than	
	absence of other			Evidence from	with an existing			harm for most	Level III-3: A
	clinical evidence.	Level 9, poor	2- Case control or	small, well-	drug with sufficient	2- Case control or		patients, be cost	comparative study
		strength, Expert	cohort studies with	designed, but not	sample size and no	cohort studies with		effective but other	without concurrent
		committees,	a high risk of	necessarily	negative studies.	a high risk of		options may be	controls. Historical
		consensus, case	confounding or bias	representative	C2: Case reports.	confounding or bias		similarily cost	control study. Two
		reports, anecdotes.	and a significant risk	samples.	One or more	and a significant risk		effective. Choice of	or more single-arm
			that the relationship		positive case	that the relationship		the intervention	studies. Interrupted
			is not causal.			is not causal.		more likely to	time series without

Grades of		Category III:	reports. No negative	<u> </u>	depend on the	a parallel control
Recommendation.	3 Non-analytic	Evidence from non-	controlled studies.	3 Non-analytic	patient values and	I
Recommendation.	studies eg case	representative	C3: Expert opinion	studies eg case	preferences and so	group.
A. At least one	_		or clinical	_	more consultation	Level IV: Case series
meta-analysis,	reports, case series	surveys, case reports.	experience.	reports, case series	should take place.	with either post-test
	4 Expert opinion	reports.	experience.	4 Expert opinion	siloulu take place.	or pre-test/ post-
systematic review, RCT, or evidence	4 Expert opinion	Category IV:	D: Inconsistent	4 Expert opinion	System above does	test outcomes.
1	Grades of	Evidence from	results. Equal	Grades of	•	test outcomes.
rated as good and	Recommendation.	expert committee	•	Recommendation.	not apply to 2009 recommendations.	
directly applicable to the target	A At least one	reports or opinions	number of positive and negative RCTs	A At least one	recommendations.	
population.	meta-analysis,	and /or clinical	and negative ACTS	meta-analysis,		
population.	•	-	F Nogotivo	systematic review of		
B. Evidence from	systematic review of	opinions of	E Negative	RCTs, or RCT rated		
well conducted	RCTs, or RCT rated	respected	evidence. Majority of RCTs show no			
clinical trials,	as 1++ and directly	authorities.	benefit over	as 1++ and directly		
,	applicable to the	Ctuameth of	placebo or	applicable to the		
directly applicable	target population;	Strength of	•	target population;		
to the target	or a body of	recommendation	comparator	or a body of		
population, and	evidence consisting	A: Category I	medication.	evidence consisting		
demonstrating	principally of studies	B Category II or	F: Lack of Evidence.	principally of studies		
overall consistency	rated as 1+	extrapolated from	F: Lack of Evidence.	rated as 1+		
of results; or	applicable to target	category I	Contract	applicable to target		
evidence	population and	C: Category III or	Grades of	population and		
extrapolated from	demonstrating	extrapolated from	recommendation:	demonstrating		
meta-analysis,	overall consistency	category I or II		overall consistency		
systematic review,	of results.	D: Category IV or	1: Category A plus	of results.		
or RCT.	D. A. b. a.d. a. C	extrapolated from	good risk benefit	D. A. brank and		
C 5 14 (B A body of	category I, II or III	ratio.	B A body of		
C. Evidence from	evidence consisting	S: Standard of good	2. Calanan A and	evidence consisting		
expert committee	principally of studies	practice	2: Category A and	principally of studies		
reports, or opinions	rated as 2++		moderate risk-	rated as 2++		
and/or clinical	applicable to target		benefit ratio	applicable to target		
experiences of	population and		2. Calana D	population and		
related authorities;	demonstrating		3: Category B	demonstrating		
indicates absence of	overall consistency		4.6-1	overall consistency		
directly applicable	of results; or		4: Category C	of results; or		
clinical studies of	extrapolated		5. C. L	extrapolated		
good quality.	evidence from		5: Category D	evidence from		
	studies rated as 1++			studies rated as 1++		
	or 1+			or 1+		
	C A body of			C A hady of		
	C A body of			C A body of		
	evidence consisting			evidence consisting		
	principally of studies rated as 2+			principally of studies		
				rated as 2+		
	applicable to target			applicable to target		
	population and			population and		
	demonstrating overall consistency			demonstrating overall consistency		
	l					
	of results; or			of results; or		
	extrapolated evidence from			extrapolated evidence from		
	studies rated as 2+			studies rated as 2+		
	l		l			

D Evidence level 3 or 4 or extrapolated evidence from studies rated as 2+	D Evidence level 3 or 4 or extrapolated evidence from studies rated as 2+	
GPP (Good Practice Point) Recommended best practice based on clinical experience of guideline development group.	GPP (Good Practice Point) Recommended best practice based on clinical experience of guideline development group.	