Appendix 3. Comparison of recommendations from schizophrenia clinical practice guidelines. Data extracted in relation to key health questions that are relevant to a clinician adopting an algorithmic approach to the pharmacological treatment of first episode schizophrenia. Where levels of evidence or grades of recommendation were attributed to a recommendation this appears in brackets beside the recommendation. See Appendix 1 Levels of Evidence and Grades of Recommendation used in Clinical Practice Guidelines for Schizophrenia in supplementary material for further information.

	PORT, 2009	Spain, 2009	Malaysia, 2009	Singapore, 2009	BAP, 2011	WFSBP, 2012	SIGN, 2013	Harvard. 2013	NICE	RANZCP, 2016
Initial presentation										
Initial oral antipsychotic for FE (Not Cloz)	FGA or SGA. Not OLZ	SGA eg Risp, Olz, Quet, Ami, Ari (A) 24-48 hour observation period with option of BDZ (C)	SGA Ami or Olz (Grade A)	SGA or FGA (A, 1++)	SGA or FGA (A). If FGA chosen this 'should probably' be a medium or low potency drug (S).	FGA and SGA both effective (A, 1). SGA preferred (C3, 4). Level of evidence available for each antipsychotic in FE Schizophrenia tabulated. Can be assumed that other antipsychotics will work but currently no evidence to make an evidence based recommendation. Olz, Risp and Quet best SGA Hpd is only FGA with evidence (Not graded)	FGA or SGA (A) Not Cloz	SGA preferably Ami, Ari, Risp, Zip. Not Cloz, Olz, Quet	Offer oral FGA or SGA	Allow drug-free assessment with BDZ for relevant symptoms* SGA (Ami, Ari, Quet, Risp, Zip) (CBR) Not Olz
Other considerations	Not Olz due to risk of metabolic side effect.	Establish a therapeutic alliance (A)			Base choice on: Relative liability for side effects especially EPSE and metabolic problems (B) Individual patient preference (S) Individual patient risk factors from side effects (B) Relevant medical history (S)	SGA chosen because of reduced risk of neurological side effects (C3, 4). Guide treatment decision by side effect profile, individual considerations.	Healthcare professionals and service users should work together to find the most appropriate medication at lowest effective dose. Discuss potential benefit and harm. Consider service user preference (GPP) Recommendations made based on specific side effect concerns of service users: Weight Gain: Hpd, Ari, Ami (A) EPSE: SGA, low potency FGA (B) TD: SGA (B) Sedation: HPD, Ari (B)		Provide information, discuss benefits and risks. Treatment should be considered an explicit individual therapeutic trial. Advise people who want to try psychological interventions alone that these are more effective when delivered in conjunction with antipsychotic medication. If the person still wants to try	Olz not recommended for initial treatment for a first episode of schizophrenia Base choice on individual preference once risks and benefits have been explained, prior response, clinical response to an adequate trial, individual tolerability, potential long-term adverse effects (EBR I)

										psychological interventions alone agree a time (1 month or less) to review treatment options including antipsychotic medication.	
Dose		Start with doses lower than recommended for multi-episode schizophrenia	Low dose (B)	Lower dose	Lower end of licensed dose range (A, 1++)	Lower end of licensed dose range (A)	Lower end of standard dose range (A, 1). Evidence for this recommendation for Hpd, Olz, Risp, only. Sparse evidence for this treatment recommendation for other antipsychotics (C1/D, 4/5)	Lowest effective (D)	Minimum effective	Start at lower end of dose range and titrate up.	Lowest effective dose (EBR, II). Target doses suggested
Dose in FE	FGA	Start at 300-500 mg Cpz Eq		300-1000mg Cpz Eq (Level 1)	300-1000 Cpz Eq (A, 1++)				300-1000 mg Cpz Eq		
	Cpz		75-300mg/day								
	Sulp		400-800mg		200-400mg						
	Triflu		10mg to start		5-20mg						
	Hpd		3-9 mg daily		5-20mg		<5mg (B, 3)				
	Olz	Lower half of dose range	5-20mg/day		10-20mg		<10mg (B, 3)		10-20 mg		
	Risp	Lower half of dose range	4-6mg		2-6 mg		<4mg (B,3)		2-6 mg		2-3mg
	Arip	Insufficient evidence for recommendation	10-15mg		10-30mg				10-15 mg		15-20mg
	Quet	500- 600mg	300-450mg		300-800mg				300-750 mg		300-400mg. Rapid dose adaptation from starting dose recommended.
	Ami		400-800ng		400-800mg						300-400mg
	Palip		3-12 mg		6-10mg						
	Asen										
	Zip	Insufficient evidence for recommendation	80mg		80-160mg				160 mg (with food)		80-120mg
	Sert		12-20mg								
Duration of initial trial of antipsychotic and when to switch medication due to non-response			4-6 weeks (Not graded)	6-8 weeks (not graded)	4-6 weeks (A, 1++)	4 weeks (A)	2-8 weeks (extrapolated from the definition of TRS, not graded) Minimum of three weeks and maximum	2-4 weeks (D)	4-6 weeks	4-6 weeks	3 weeks

						of 6 weeks described in a different section (not graded)				
Duration of initial trial of antipsychotic medication trial where there is a partial response						4-10 weeks and 5-11 weeks for the second antipsychotic (not graded)	8 weeks (D)			6-8 weeks
Second line antipsychotic medication	FGA or SGA	SGA eg Risp, Olz, Quet, Ami, Ari (A)	Switching to atypical confers no advantage in terms of quality of life (Grade A).	SGA or FGA (D, 4)	SGA or FGA. Should use an AP with a favourable efficacy profile before moving to clozapine (A)	SGA if initial antipsychotic was FGA (B, 3)	FGA or SGA (extrapolated from definition of TRS)	FGA or SGA. Prefer Risp, Olz or FGA if not previously used. If one was used in initial treatment then use any AP except Cloz.	Offer oral FGA or SGA	Another SGA including option of Olz
Duration of second trial of antipsychotic medication		6-8 weeks (C) Although in the algorithm it states 4-6 weeks (not graded)	6-8 weeks (Not graded)			2-8 weeks (extrapolated from the definition of TRS, not graded) 5-11 weeks for the second antipsychotic if partial response (not graded)		4-6 weeks		
Role of long acting injection or depot antipsychotic	For maintenance treatment if preferred to oral	Reserved for those who choose this route. Those who repeatedly fail to adhere despite psychosocial and interventions aimed at adaptation and adherence (C in one section and B in another) If there is no response to treatment or low adherence with frequent relapses, low dose first generation depot antipsychotics should be tried for a period of 3-6 months (C).	If non-adherent (Grade A in one section and Grade B in another section)	If patient preference or if treatment adherence is an issue (C, 2+) Not for acute episodes because they may take 3-6 months to reach steady state (B, 2++)	Role uncertain for FE schizophrenia. Patient-specific intervention for improving adherence or if preference of patient (S)	Good evidence for FGA depots in relapse prevention (A,1) but no clear difference in efficacy between oral and depot (A,1) Good evidence for Risp LAI in relapse prevention (A,1) and some evidence of superiority over oral formulation (C,4). Also some evidence for use in FE (B,3) Evidence for Pal LAI (A,1); Olz LAI (A/B, 2/3)	Service user preference, medication adherence difficulties (B)	Not routine use. If non-adherent. Although may be necessary to ensure an adequate trial for the initial antipsychotic stage of an episode of FE schizophrenia.	Patient preference. When avoiding covert non-adherence is a clinical priority	If poor or uncertain adherence or if persons preference or poor response to oral medication (EBR II)
Combination antipsychotics		Not recommended	Monotherapy whenever	Not recommended except for switching	High dose or combined AP for	Monotherapy recommended (C3, 4)	Should not be routine. If considered	Cloz augmentation.	Do not initiate. Check PRN use of	If adequate response is not

		except when switching (B)	possible (Grade A in one section and Grade C in another) Combination with clozapine may be considered (Grade A)	or clozapine augmentation (B, 2++)-	TRS only after failure of several, adequate sequential trials of AP monotherapy and other evidence based treatments for TRS including clozapine (B). If used use a closely monitored, time-limited trial (D).	May be advisable in some individual circumstances (C3,4). Monitor at frequent intervals (C3,4) Cloz augmentation	for an individual situation, discuss benefits and harms with service user (GPP) Cloz augmentation as above	Or an option if augmentation strategies with cloz have not worked.	AP. Clozapine augmentation strategy.	achieved after monotherapy treatment trials of two antipsychotic agents given separately at therapeutic doses, antipsychotic polypharmacy may be justifiable but requires careful monitoring (EBR II)
Maintenance of remission										
Duration of maintenance treatment following a first episode of schizophrenia		12 months (C)	1-2 years (not graded)			Treat for at least one year (C,4)	At least 18 months (D)		High risk of relapse if discontinued in next 1-2 years	Provide an adequate duration of treatment (EBR II) A minimum of 12 months following remission is suggested in the text (not graded). Continue to engage with first episode for schizophrenia service for at least 2-5 years (EBR II)
Choice of AP for maintenance	FGA or SGA	Continue with treatment used in acute phase (not graded).	Use AP for relapse prevention (Grade A) No difference amongst Aps in efficacy for relpse prevention (Grade A)	Same as used for acute phase (A, 1+)	Antipsychotic medication required (A) Consider factors as for first episode plus: Prior treatment response (S) Experience of side effects (S) Level of medication adherence (S). Comorbid physical illness (S) Long term treatment plan (S).	SGA because: Evidence for superiority of Risp, Olz and Sert for treatment discontinuation and relapse prevention (B,3). Reduced risk of motor side effects (C,4) Some advantage in reducing negative symptoms (C,4) Use antipsychotic with best	Offer maintenance with antipsychotic (A) Use medication that was used during acute phase assuming efficacy and tolerability (GPP) Olz, Ami, Risp preferred with CPZ and other low potency FGA an alternative (B)	Not Quet		

						benefit/tolerability profile in acute phase (Good clinical practice)				
Dose of maintenance medication following a first episode of schizophrenia (evidence from multi-episode schizophrenia)	300-600 mg Cpz Eq. SGA dose effective in acute phase			Dose should not be lower than half of the effective dose used in the acute phase (A, 1+)	Any reduction in dose should be closely monitored. Consider risk of destabilisation (C)	<600 mg Cpz Eq. FE patients require lower doses than multi-episode (C,4) Dose in accordance with stabilisation dose (C,4)	300-400 mg CPZ Eq, 4-6 mg Risp or equivalent (B)			
Targeted intermittent dosing strategies	Not recommended in preference to continuous maintenance treatment regimens due to risk of relapse.				Should not be used in preference to continued AP treatment (B).	Continuous use for relapse prevention strongly recommended (A,1). Consider if patient unwilling to accept continuous maintenance or side effect sensitivity			Not routinely. Consider if patient unwilling to accept continuous maintenance or side effect sensitivity.	
Treatment resistance										
When to offer a trial of clozapine										
If non-response following adequate trial of two AP's one of which is an SGA	Yes	Yes (A)	Yes (Grade A)	Yes (A, 1++)	Yes (A)	Yes (B,3)	Yes (B)	Yes	Yes	Yes (EBR I)
Other considerations regarding clozapine use	Trial clozapine for hostility or violent behaviour. Trial of clozapine for those who exhibit significant or persistent suicidal thoughts or behaviours.	Also indicated in persistent or high risk of suicide despite treatment for depression if present (A). SGA eg Olz and Risp trial before diagnosing TRS (C).	Clozapine superior in treating persistent aggression (Grade A) Clozapine indicated in treatment of persistent suicidal thoughts or behaviours (Grade A)		Consider trial for aggression or hostility (B). Consider if persistent substance misuse (D). Consider if intolerant to neurologic side effects of antipsychotics (A).	One SGA previously. Non response to two antipsychotics in previous 5 years. Trial at adequate dose for 2-8 weeks. (not graded) If intolerant to Cloz, try Olz or Risp (B,3). Consider Cloz if significant and continuous increased risk of suicide (B,3) Cloz may reduce craving in concurrent	One SGA in previous trial (B) If TRS accompanied by aggression/ hostility consider clozapine (D)	Previous trial of Risp, Olz or FGA More effective if presentation includes hostility and for suicide prevention.	One SGA in previous trial	When treatment resistance has been clearly demonstrated, clozapine should be offered within 6-12 months. (EBR, I) In another section an evidence level of EBR II is attached to the statement 'treatment resistant disease should be recognised within

						alcohol use disorder (B,3); and other substance use disorder (C3,4) but consider risk of non-compliance.				6-12 months of starting potentially effective antipsychotic treatment and confirmed as soon as possible.
Clozapine dose	Blood level > 350ng/ml. 300-800mg/ day	200-450mg/day		Blood level > 350ng/ml. 100-450 mg/ day (Recommendation not graded)	Plasma level can guide dose (D)	Blood level > 350ng/ml. 100-900mg/ day (B/C3; 3/4)		Blood level 350-450ng/mL Usual dose 300-400mg/day		
Adequate duration of clozapine trial?	At least 8 weeks	4-6 weeks (Not graded)			3-6 months (B)		NR			If possible a trial of clozapine should be continued for 12 months to allow for late responders (EBR I).
Clozapine augmentation strategies		Addition of a second SGA (C)	Combination with of AP clozapine may be considered (Grade A) Clozapine + ECT (Not graded)	Another AP or ECT (Recommendation not graded)	Only consider if optimised clozapine treatment for minimum of 3 months (S). Use medication that has complementary receptor profile and does not dose not compound SE (B)	Some evidence for adding SGA (C,4) Ltg augmentation might improve symptoms (B,3).	Add other SGA for trial period (C) Consider trial of Cloz + Ltg (B)	Add Risp; add other AP, LTG,	Add other AP considering SE profile	Adjunctive medication with clozapine or reinstate most efficacious previous treatment and add adjunctive medication (EBR II).
Duration of trial of augmentation strategy?					At least 10 weeks (B)		10 weeks for augmentation with SGA (C)		8-10 weeks	
High dose antipsychotics					Not recommended unless all evidence based treatments for TRS have been optimised and failed. Time limited trial (B) Continue after 3 months only if benefit outweighs risk (S).	Not recommended (not graded)	Trial if clozapine and augmentation strategies have failed (D). Need to develop local guidelines for monitoring (GPP)	Not recommended	Do not use loading dose. Caution with additional PRN AP's	

Unsatisfactory improvement despite clozapine augmentation			Information appears in algorithm not in main text and is not graded. AP combinations, AP + ECT, AP + mood stabiliser.	AP combinations AP + ECT AP plus another augmenting agent e.g. mood stabiliser. (Recommendation not graded)		Inconsistent evidence for memantine in TRS (D,5)		Options presented below. Note sparce evidence. Not listed in order of preference. Try a different clozapine augmentation strategy. Add mementine or omega 3 fatty acid to clozapine. Stop cloz and try AP not previously tried. Stop Cloz. Try combination of FGA and mirtazapine or celecoxib. Try combinations of AP not including cloz.		

Abbreviations: AP= Antipsychotic; CPZ Eq = Chlorpromazine Equivalents; ECT = electroconvulsive therapy; EPSE = Extrapyramidal side effects; FE = First Episode; FGA = First generation antipsychotic; LAI = Long Acting Injection; PRN = 'Pro re nata' as required; SE = side effect; SGA = Second generation antipsychotic; TD = Tardive Dyskinesia; TRS = Treatment resistant schizophrenia

Medications: Ami= Amisulpride; Ari = Aripiprazole; BDZ = Benzodiazepine; Cloz = clozapine; CPZ = chlorpromazine; Hpd = haloperidol; Olz = Olanzapine; Palip= Paliperidone; Quet = Quetiapine; Risp = Risperidone; Sert= sertindole; Sulp= sulpiride; Triflu = trifluperazine; Zip = ziprasidone